A PROSPECTIVE OBSERVATIONAL STUDY OF THE FOLLOW UP OF MEDICAL MANAGEMENT OF EARLY PREGNANCY FAILURE.

DISSERTATION SUBMITTED IN THE PARTIAL FULFILMENT OF THE REQUIREMENT OF TAMIL NADU DR. MGR MEDICAL UNIVERSITY FOR THE DEGREE OF MS BRANCH II (OBSTETRICS AND GYNAECOLOGY) EXAMINATION TO BE HELD IN APRIL 2017.

DECLARATION CERTIFICATE

This is to certify that the dissertation entitled "A PROSPECTIVE OBSERVATIONAL STUDY OF THE FOLLOW UP OF MEDICAL MANAGEMENT OF EARLY PREGNANACY FAILURE" which is submitted by me in partial fulfillment towards the M.S. Branch II (Obstetrics and Gynaecology) Degree examination of The Tamil Nadu Dr. M.G.R. Medical University, Chennai to be held in April 2017, comprises only my original work and due acknowledgement has been made in text to all materials used.

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CERTIFICATION

This is to certify that the dissertation entitled “A PROSPECTIVE OBSERVATIONAL STUDY OF FOLLOW UP OF MEDICAL MANAGEMENT OF EARLY PREGNANCY FAILURE” is the original work of Dr. Pushplata Kamari towards the M.S. Branch II (Obstetrics and Gynaecology) Degree Examination of The Tamil Nadu Dr. M.G.R. Medical University, Chennai to be held in April 2017.

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A prospective observational study of the follow up of medical management of early pregnancy failure.

Dr. PushplataKumari, PG Registrar, Emp. No.32380, Dr. Jiji Elizabeth Mathew, Professor, Emp.no.13790, Dr. Anuja Abraham, Assistant professor, Emp.No.31916, Dr. Santosh Benjamin, Associate Professor, Emp. No.31318, Dr. Swati Rathore, Associate Professor, Emp. No.31682, Department of OG - 5.

Ref: IRB Min No: 9691 [OBSERVE] dated 20.10.2015

Dear Dr. Pushplata Kumari,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "A prospective observational study of the follow up of medical management of early pregnancy failure" on October 20th 2015.

The Committee reviewed the following documents

1. IRB Application format
2. Patient Information Sheet and Informed Consent Form (English, Tamil, Hindi)
3. Proforma
4. Cvs of Drs. PushpalataKumari, Jiji Elizabeth Mathew, Anuja Abraham, Santosh Benjamin, Swati Rathore
5. No. of documents 1 – 4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on October 20th 2015 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "A prospective observational study of the follow up of medical management of early pregnancy failure" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in)

Yours sincerely

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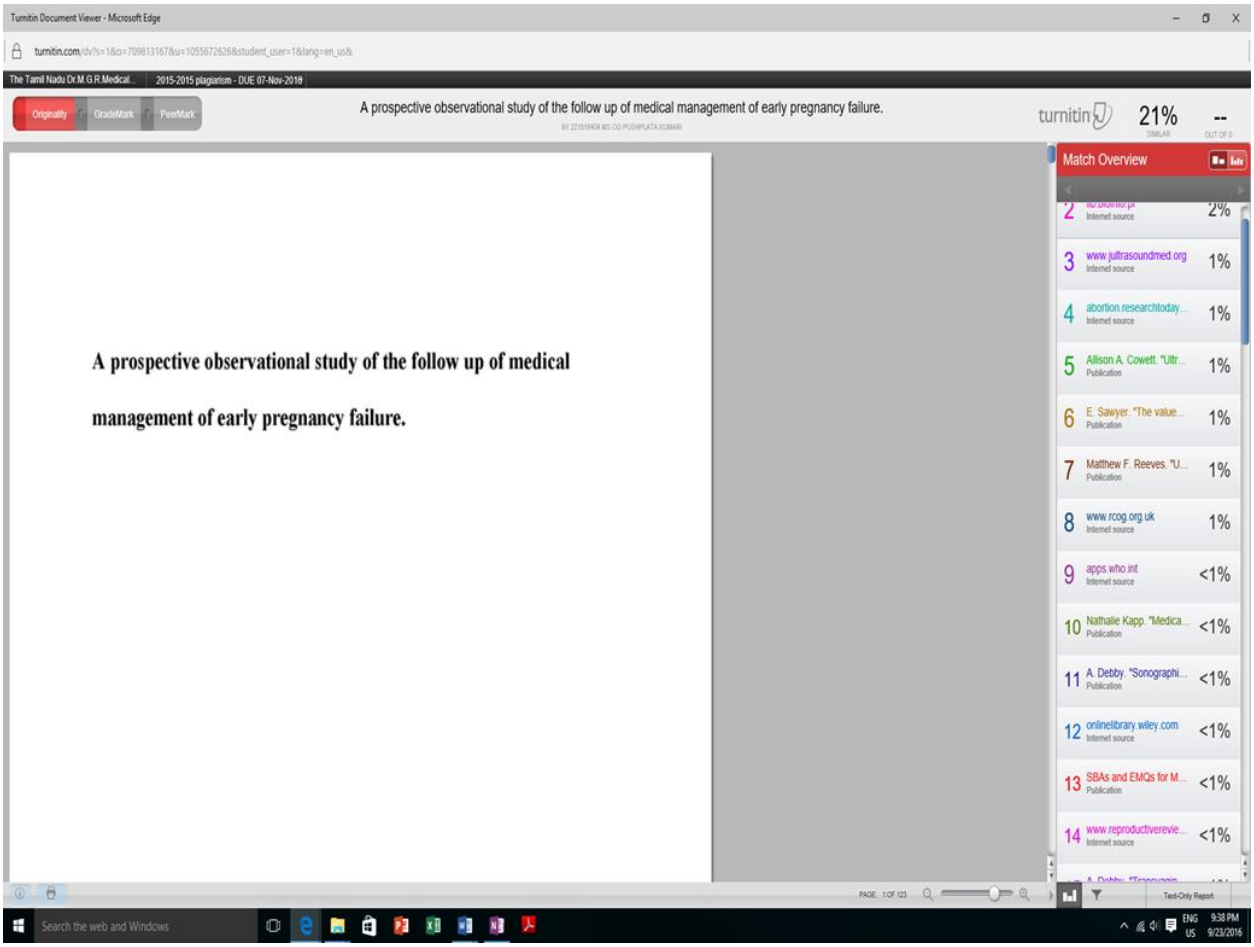
PLAGIARISM CERTIFICATE



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ABBREVIATION

- WHO: World Health Organization
- ACOG: American College of Obstetrics & Gynaecology
- RCOG: Royal College of Obstetrics & Gynaecology
- NICE: National Institute of Clinical Excellence
- D & C: Dilation and Curettage
- EVA: Electric Vacuum Aspiration
- MVA: Manual Vacuum Aspiration
- RPOC: Retained Product of Conception
- PGE1: Prostaglandin E1
- β hCG: Beta human Chorionic Gonadotrophins
- TVS: Trans Vaginal Ultrasonography

Contents

INTRODUCTION

American College of Obstetrics and Gynaecology(ACOG) defines early pregnancy loss as "a nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus without fetal heart activity during first trimester" (1). It affects one in four women and is one of the most common complication of pregnancy (2).

Early pregnancy loss below 14 weeks can be managed both medically and surgically. Misoprostol regimen is currently the recommended medical management of early pregnancy failure. It is speculated that 29% of women will have incomplete evacuation by day 3 of misoprostol and may need curettage. (3) Clinical and sonologic features that would help us to decide the need for curettage are still not well established. Hence, management is individualized.

After treatment with various regimen of misoprostol, patients who expel the sac or fleshy mass in toto and have minimal bleeding per vagina, presumed to have complete expulsion clinically. The patients with incomplete expulsion have active bleeding per vagina with an open cervical os. They need surgical evacuation. Usually ultrasound examination are done to confirm the complete expulsion. However, the ultrasound findings that would predict the presence of retained product of conception (RPOC) are not well established. The ultrasound findings commonly taken in consideration for diagnosis of incomplete evacuation are endometrial thickness, irregularity of the endometrial lining and the

echogenicity of the content. After that modality of treatment, surgical evacuation or repeat the doses of misoprostol or no further treatment is decided on individual basis.

Numerous studies have looked at the endometrial thickness, volume of the endometrium and echogenicity of contents but no definite conclusion has been made to diagnose RPOC. (4–7) The implication of minimal retained products in the absence of sac is uncertain.

Hence, this prospective observational study intends to find out the clinical and sonologic findings after medical method of termination of early pregnancy loss before discharge of the women that can diagnose the complete expulsion and avoid the unnecessary surgical evacuation. It also includes finding out the clinical predictors that can find out the factors that help in complete expulsion after medical method of termination.

AIMS AND OBJECTIVES

Primary Objective

- To study the need for further treatment following discharge after medical management for early pregnancy loss.

Secondary Objective

- To find out the clinical predictors that can help in predicting complete expulsion after medical method of termination.

REVIEW OF LITERATURE

Introduction

Early pregnancy loss or miscarriage, is defined as a "nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus without fetal heart activity during first trimester" (1). The first trimester pregnancy loss affects 10-20% of pregnant women and is one of the common complication of pregnancy (2).One out of four women experience early pregnancy loss during first trimester in their life time. These losses are spontaneous abortion, anembryonic gestation, and embryonic or fetal death. Loss of pregnancy symptom with vaginal bleeding are suggestive of miscarriage.

Clinical history with digital vaginal examination are the usual mode of diagnosis but the accuracy of these findings is only 50 % (8). In modern practice transvaginal ultrasonography is accepted standard test for diagnosis of early pregnancy loss (9). Biochemical tests like maternal serum beta human chorionic gonadotropin (β hCG) and serum progesterone is not routinely used for diagnosis of early pregnancy failure. However, in case of women with inconclusive ultrasound findings, the declining level of serum β hCG can help to diagnose early pregnancy loss with the sensitivity of 93-97% (10).

Different modalities of treatment can be used in women with incomplete expulsion of product of conception after diagnosis of early pregnancy loss. The different modalities of management are expectant management, medical method and surgical method. Different

studies have proven the effectiveness of these methods either alone or in combination. Approximately, 6-8% of these women have delayed complications like persistent spotting per vagina, fever due to retained product of conception (RPOC) and chronic pelvic pain (11). These complications are found to be more with medical method than the surgical method of management (12). RPOC increases the morbidity and mortality of the women as there is risk of chronic endometritis, sepsis and development of intrauterine adhesion causing menstrual problems.

Incomplete expulsion can be diagnosed clinically but sonographic features have better accuracy. Hence, ultrasound is done before proceeding to any further intervention. There are different sonographic findings like endometrial lining of varying thickness echogenic area in the endometrial cavity and increased intrauterine vascularity which are suggestive of RPOC. However, the sensitivity of ultrasound features to predict RPOC is still questionable, and false positive diagnosis lead to unnecessary intervention in the form of repeat surgical evacuation.

Epidemiology

Spontaneous abortion is the most common complication of early pregnancy. In 2003, the prevalence of abortion as reported in Centers for Disease Control and Prevention (CDC) was 26% at less than 6 weeks of gestation, 18% at 7 weeks, 15% at 8 weeks, 18% at 9-10 weeks, 9.7% at 11- 12 weeks (13). According to population based survey done worldwide in 1995 the estimated rate of abortion was 35 per 1000 women aged 15-44 years (14). However, the frequency decreases with increasing gestational age.

The risk of spontaneous abortion is influenced by previous reproductive outcome of the women. In primigravida and women with a history of successful pregnancies, the incidences of abortion were 4-5%. Whereas, women with two or more abortion had greater 24% risk of aborting the present pregnancy. The risk is 5% in women after one term pregnancy as compared to 19% who had previous abortion (15).

Definition and terminology

The description of early pregnancy loss is not very clear, as there is no standard definition. Various authors have used different terminology to describe early pregnancy loss. Standardization of the term for early pregnancy loss is needed to allow the clinician to compare the outcome after different modalities of treatment. Before the use of ultrasound, the term threatened abortion was used for any bleeding in early pregnancy with closed cervix (16).

Gradually with the increasing use of ultrasound, different terms like non-viable pregnancy, incomplete miscarriage was used. Mathew Duncan, in 1874, has first described the term missed abortion as a clinical entity in which, "the fetus died before viability with no effort at its expulsion by the uterus" (17). As this definition did not describe the duration of retention of embryo, slowly this definition was disputed. Later different terminology like chemical pregnancy (18), blighted ovum (19), embryonic gestation (20), impending abortion (21) and first trimester intrauterine fetal demise (20) were used. Jauniax and colleagues (22) has simplified description of early pregnancy loss based on the stage of the process of expulsion and the time to presentation to the physician is complete pregnancy

loss, incomplete pregnancy loss and delayed pregnancy loss and this is described in Table 1 (23).

Table 1: Classification of First Trimester Pregnancy Loss

Diagnosis	Characteristics
Complete pregnancy loss	• Complete passage of product of conception with closed cervix. • Endometrial thickness typically < 15mm
Incomplete pregnancy loss	• Partial passage of products of conception with closed or open cervix. • Any endometrial thickness • Presence of central heterogeneous echogenicity or presence of gestational sac
Delayed pregnancy loss	• No history of tissue passage with closed cervix. • Gestational sac > 20 mm with no fetal pole or yolk sac. • Gestational sac < 20 mm with no change in size over 7 days • Fetal pole > 6 mm with no detectable fetal heart activity • Fetal pole < 6 mm with no change over 7 days

Complete pregnancy loss is defined as complete passage of intrauterine content. The cervix is closed and the remaining endometrial thickness is less than 15 mm by transvaginal

ultrasonography. An incomplete pregnancy loss is characterized by partial passage of intrauterine content with clinical or ultra sonologic feature of retained product of conception. The term delayed pregnancy loss was previously referred to as blighted ovum, anembryonic pregnancy, missed abortion or failed pregnancy. The cause of first trimester pregnancy loss is multifactorial, but certain associated factors increase the risk (24). These factors are the following:

- Advanced maternal age
- Women with low Body Mass Index (BMI)
- Women with elevated cortisol level
- Low progesterone level
- Poor glycemic control
- History of smoking
- Thyroid dysfunction
- Obesity
- Acute infection with toxoplasmosis, Parvovirus B12.

Management option for first trimester pregnancy loss

Once a spontaneous early pregnancy loss has been diagnosed, there are three different modalities of management: Expectant, Medical, or Surgical. The mode of management is determined by patient preference, gestational age, maternal hemodynamic stability, presence of infection and type of pregnancy loss.

Expectant management

Expectant management is an option commonly chosen by women who do not want any intervention and instrumentation. In this approach patient is allowed to wait for spontaneous expulsion. However, the duration of complete evacuation varies from 1 week to 1 month. One of the largest observational study by C. Luise et al evaluated the outcome of expectant management of early pregnancy loss.1096 consecutive women with suspected first-trimester miscarriage were followed up to four weeks. Women who did not have a complete miscarriage (n = 686) were offered expectant management or surgical evacuation. Successful spontaneous abortion occurred in 81% women who were managed expectantly (25).

In 1995, Sven Nielsen et al had prospectively randomized 155 women with early pregnancy loss less than 13 weeks into expectant management or D & C (Dilation and curettage) in a ratio of 2 to 1. The women were examined by transvaginal ultrasonography after 3 days and at 2 weeks. If examination showed retained tissue with anteroposterior diameter more than 15 mm, they underwent Dilation and Curettage (D & C). Seventy-nine percent of the patient, randomized to expectant management, had spontaneous resolution by day 3. Although the duration of vaginal bleeding was longer (mean 1.3days) in expectant management group than the D & C group ($p < 0.01$), it had not shown decrease in the packed cell volume (PCV). They concluded that expectant management and D&C had no difference in the outcome (4).

The type and stage of pregnancy loss should also be considered while counseling for method of termination. The success rate with expectant management is better with an incomplete pregnancy loss than delayed pregnancy loss (85% vs 33% completion) (26).

Chipchase J et al randomized 35 women with RPOC after spontaneous abortion in to expectant or surgical group. They reviewed women at 1st week, 2nd weeks and 4th months. Women were observed for bleeding, the number of days of pain, duration of sick leave and return to normal periods. There were no significant differences between the two groups. 75% of the women, who attempted to conceive successfully did so by 6 months in the expected group and 66% in the surgical group (27).

Of all the study of expectant management of women with early pregnancy loss only three are randomized study (4,26,27), rest of the studies are either observational (28) or case control report (21). The success rate of expectant management reported in the randomized study (4,26,27) was 79% and 100 % for incomplete and inevitable abortion respectively. The success rate reported in non-randomized trials varied from 91% and 100%.

Surgical management

Surgical method for pregnancy termination in first trimester pregnancy loss include dilatation of the cervix followed by sharp curettage (D & C) or by electric vacuum aspirator (EVA), or manual vacuum aspiration (MVA) or a combination of these methods.

These procedures can be done under intravenous conscious analgesia either in the in-patient setting or in the procedure room in the office clinic. EVA is performed in the

operating theater under general, spinal anesthesia or epidural analgesia with electric vacuum device and rigid cannula. MVA can be performed in the outpatient clinic under local analgesia with flexible cannula attached to 60 ml syringe that can create negative suction pressure. MVA is recommended for pregnancy loss at less than 12 weeks. Complete evacuation is seen in 80-100% of women undergoing surgical method (29). Cervical ripening agent prior to these procedures helps in patient comfort and reduces the difficulty in evacuation. Meta-analysis of different agents (PGE1, mifepristone, osmotic dilator) used for cervical ripening had shown equal efficacy (30). Prophylactic antibiotics are recommended before the procedure. Potential complications associated with surgical modalities are anesthesia related complication, uterine perforation, cervical tear, infection and intrauterine adhesion affecting the future fertility.

The studies comparing between MVA or EVA for treatment of early pregnancy loss have shown that MVA are associated with less expense, duration of procedure, procedure related complications, and blood loss (29,31,32). The success rate reported for complete evacuation after early pregnancy loss with ranges from 95-98% for MVA and 97-98% for EVA.

Medical management

Medical management has been shown to be an excellent method management of early pregnancy loss for women desiring minimal intervention. Since the prehistoric era various agents have been used for the medical termination of pregnancy. The agents used in the

modern era are various injectable agents in the amniotic cavity like hypertonic saline, urea, ethacridine lactate and prostaglandin. Some agents like ethacridine lactate, prostaglandin instilled into the extra amniotic space-using catheter. Prostaglandins and oxytocin are used as intramuscular injection. Various prostaglandin agents and their analogue are used by vaginal, buccal or bilingual route. However, the most effective method is the regimen using Misoprostol.

Agents used for medical methods:

Mifepristone:

Mifepristone is progesterone receptor antagonist, which act after attaching to the receptor, causes breakdown of maternal capillaries in the decidua, and increases synthesis of prostaglandin by the epithelium of decidua glandular cells (33). It also affects the sensitivity of prostaglandin to the uterus. All these effect appear within 24-48 hour of their use. Some of the dosage regimens for medical management of early pregnancy loss include mifepristone in combination with misoprostol. Oral Mifepristone 200 mg, 24-36 hours before misoprostol, 800 µg, result in an overall expulsion success rate of 91-96% (34). It is expensive and is always used in the combination with misoprostol. Qian et al had shown in the multicenter randomized study that abortion rate was higher in vaginal misoprostol than the oral Mifepristone group (98.1% vs 94.0%, p value= 0.023) and there was no difference in the induction to abortion interval at different gestational age. This study showed that the misoprostol only regimen is effective (35).

Misoprostol

A synthetic analogue of prostaglandins E1 (15-deoxy-16-hydroxy-16-methyl PGE1) was developed for prevention of peptic ulcer because of mucosal protective properties (36). It also has effect on the softening of the cervix and initiation of uterine contraction. It can be used orally, vaginally and sublingually. This analogue differ and better than other analogue of prostaglandin in that;

- less expensive
- orally active and effective in multiple route of administration,
- can be stored in the room temperature without change in the efficacy and
- Has low rate of dose dependent risk.

Randomized controlled trial had shown the efficacy for complete evacuation with vaginal misoprostol compared to placebo (80% versus 16% p value <0.01) and lesser need for surgical evacuation (28% versus 84% p value <0.001) (37).

There are various route of administration of misoprostol but study had shown that the most effective route is vaginal and sublingual followed by oral (38,39).

In a randomized controlled equivalence trial, Von Hertzen et al, in 2007, had compared the efficacy of two different routes and intervals of misoprostol for termination of early pregnancy. This was a multicenter trial done in 11 teaching hospitals from six countries including India. Two thousand sixty-six women with 63 days or less of gestation requesting for medical method randomly assigned to the four treatment groups (three doses of 800-mcg misoprostol given sublingually at 3-hour intervals, vaginally at 3-hour interval,

sublingually at 12-hour interval, and vaginally at 12-hour interval). There was no difference in the complete abortion rates at 2-week follow-up in the sublingual group and the vaginal group when misoprostol was given at 3 hour intervals (difference 0.4%, 95% CI – 4·0 to 4.9, p value = 0.85 equivalence shown). They had shown a statistical significant difference in the complete abortion rate between the sublingual and vaginal 12-h groups (4.6%, 95% CI –0·2 to 9.5, p value =0·06, equivalence not shown).

The percentage of women who continued pregnancy were almost similar in 3 hour groups irrespective of route of administration (difference 1·8 %, 95% CI –0·8 to 4.4, p=0.19). However, in the 12-h groups significantly higher percentage of women continued pregnancy in sublingual route in comparison to vaginal (difference (4.4%, 95% CI 1.2-7.5, p=0.01). They suggested vaginal route of administration for 12 hourly intervals and for 3 hourly intervals either route could be considered (40).

Misoprostol is a well-tolerated and safe drug. Fever and chills have been reported after high doses. Oral administration was associated with higher incidence of diarrhea and longer duration of induction to abortion interval than the vaginal one. Several randomized trial showed vaginal route of misoprostol alone were more effective and associated with lower incidence of side effect than the oral or sublingual route. (41)

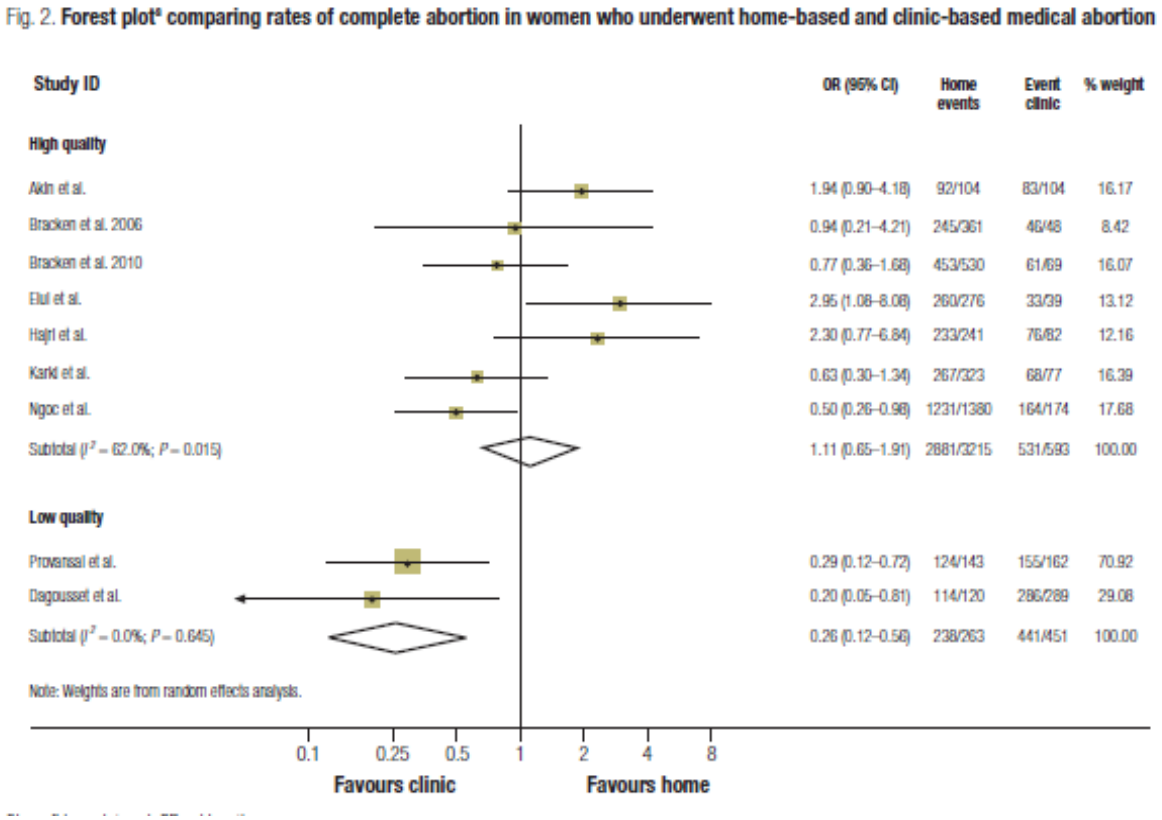
The other benefit with the usage of misoprostol is that it can be self-administered and can be used in the low resources setting where the access to health care is limited. The safety and effectiveness of abortion with misoprostol was compared in a multicenter randomized controlled equivalent trial by Kleinberg-Allvin et al in six district level center of Uganda

from April 2013 to July 2014 by physician and midwives. One thousand and ten women with signs of incomplete abortion like bleeding during pregnancy, open cervical os and partial expulsion were included and randomized to receive misoprostol by either physician or midwives in 1:1 ratio. The model-based risk difference for midwives' verses physician group was -0.8% (95% CI -2.9 to 1.4) which was falling within the predefined equivalence range (-4% to 4%). Hence, study concluded that the treatment of incomplete abortion with misoprostol by midwives are equally safe and effective and can be used in the low resources setting (42).

The systemic review by Thoai D Ngo et al, in 2010, had compared the effectiveness, safety and acceptability of medical method at home or clinics. The data from nine prospective cohort study (n=4522 participants) comparing the home based and clinic based medical abortion was collected. The analysis had shown that the average success rate for complete abortion in women who took misoprostol at home was better than those who took in clinics (86-97% versus 80-99% 95% CI: 88.7–90.7%).

Women were more satisfied (which was assessed by acceptability of the method; the likelihood of choosing the method again; and the likelihood of suggesting medical abortion to a friend) with home based medical abortion than clinics based. Their average satisfaction rate was 85.6% (95% CI: 82.6–87.4). Side effects were inconsistently reported across these studies (43).

Figure: 1 Forest diagram of the outcome of all studies.



The consensus for the using misoprostol alone or in combination with mifepristone and doses regimen is not universal. Depending on the gestational age, RCOG and WHO recommend different regimen for termination of pregnancy. They recommend different dose regimen of mifepristone followed by misoprostol

<u>Other prostaglandin analogue:</u>

The commonly used prostaglandin analogues are carboprost, sulprostone, gemprostone, and misoprostol. Carboprost is an F2 alpha prostaglandin analogue and is infrequently used due to high side effect profile. Sulprostone is an E2 analogue and is associated with a unique complication of coronary spasm hence banned for their usage. Gemprostone and

misoprostone are E1 analogue and are the most commonly used agents. Both has demonstrated high efficacy and shorter induction to abortion interval when compared to extra amniotic saline or intra amniotic PGE2. However, in the study comparing the PGE1 and misoprostol, misoprostol is shown to equal or more efficacious than the gemprostone.

Comparison between the methods for termination:

Various trials have compared different methods for termination of pregnancy during first trimester loss regarding effectiveness and acceptability. The main multicenter randomized trials are shown in Table 2 (3,44–46).

Table: 2 Multicenter trial comparing different methods for termination of pregnancy at first trimester loss

Trial / Author	**Intervention**	**Primary outcome**	**Results**
MIST trial *J.Trinder et al* (44)	Surgical versus Expectant / Medical	Gynecological infection, unplanned hospital admission, Unplanned curettage.	Risk of infection within 14 days: • Surgical and expectant (risk difference 0.2%, 95% CI -2.2 to 2.7%) • Medical and surgical (risk difference 0.7%, 95% CI -1.6% to -3.1%) Unplanned hospital admission: • Expectant group: risk difference -41%, (95% CI -47% to -36%) • Medical group: risk difference -10 %, (95% CI -15% to -6%) Unplanned curettage: • Medical group: risk difference -39%, 95% CI -44% to -34%) • Expectant group: risk difference -30% 95% CI -35% to -25%)
Medical vs surgical method *Jun Zhang et al* (3)	Surgical vs Expectant	Efficacy, safety and acceptability of treatment	• Complete expulsion by day 3 and 8 in medical group: 84% (95% CI 81-87%) • Treatment failure by day 30: 16% in medical group and 3% in surgical group (absolute difference 12%,95% CI 91)
Trial / Author	**Intervention**	**Primary outcome**	**Results**

TOPS trial *Robson SC et al* (45)	Medical vs Surgical	To determine the acceptability, efficacy and costs of medical and surgical termination of pregnancy (MTOP & STOP) at less than 14 weeks' gestation	MTOP: • More negative experiences of care and lower acceptability. • Acceptability declined with increasing gestational age. • Less costly and less effective than STOP. The majority of women who had chosen MTOP were satisfied with their care and found the procedure acceptable.
MisoREST trial *Marianne AC Verschoor et al* (46)	Expectant vs Medical	Cost and effect of treatment	In progress

Systematic reviews of randomized trials of women with first-trimester missed abortion of different method of termination

Expectant, medical, or surgical management of first-trimester miscarriage: a meta-analysis.

Sotiriadis A. et al had included 27 randomized and quasi-randomized trials that looked at women with first-trimester pregnancy loss with surgical, medical, or expectant management. The objective of the systematic review was to quantify the relative benefit and harm of different management option of first trimester pregnancy loss. The data were collected from EMBASE, MEDLINE, and Cochrane Controlled Trials Register searches (1966 to July 2004). Primary outcomes were successful treatment and patient satisfaction and the secondary outcomes were bleeding (moderate to severe), blood transfusion, emergency curettage, nausea, vomiting pelvic inflammatory disease, and diarrhea.

With surgical method there was significantly more complete uterine evacuation than the medical method (risk difference 32.8%, number needed to treat 3).The success rate of medical management was higher (62%) as compared to expectant management (39%) (Risk difference 49.7%, number needed to treat 2). Sub analysis of cases with incomplete miscarriage showed that medical management had two-third chance to achieve complete evacuation in comparison to surgical management. Nevertheless, medical management had better chance than expectant management. Analysis of the data from the studies that had evaluated outcome at forty-eight hours or more after allocation was done separately. It showed that the success rate was better with medical management than expectant

management. The success rate was much lower with expectant management in comparison to surgical evacuation. There were very little data about patient satisfaction. Patient satisfaction data were inconclusive. The risk of moderate or severe bleeding was lower with medical management than expectant management (risk difference 3.2%) and surgical management (risk difference 2.1%) (47).

Expectant care versus surgical treatment for miscarriage: a systemic review (48)

Nanda K et al conducted a Cochrane systemic review with the objective to compare the safety and effectiveness of expectant versus surgical management for early pregnancy failure. Seven randomized trials, with 1521 participants, that compared expectant treatment to surgical treatment (vacuum aspiration or dilation and curettage) for miscarriage were included.

The outcomes were:

- The risk of incomplete miscarriage at two (RR 3.98; 95% CI 2.94 - 5.38) and six weeks (RR 2.56; 95% CI 1.15 - 5.69) were higher in the expectant-care group.
- The expectant-care group had greater need for unplanned surgical treatment (RR 7.35; 95% CI 5.04 - 10.72).
- The expectant-care group had longer duration of bleeding (MD 1.59; 95% CI 0.74 - 2.45) and similarly more need of blood transfusion (RR 6.45; 95% CI 1.21 - 34.42).
- The risk of infection was similar in both the groups (RR 0.63; 95% CI 0.36 to 1.12).
- Pregnancy data were limited.

- The costs were lower for the expectant-care group.

Medical treatments for incomplete miscarriage: a systemic review (49).

Neilson JP et al, in a systemic review, had included fifteen randomized controlled trials (including 2750 women). Medical treatment was compared with expectant care or surgery. The objective was to assess the effectiveness, safety and acceptability of any medical management for incomplete miscarriage below 13 weeks

Three trials that compared misoprostol (all vaginally administered) with expectant management found no significant difference in rate of complete miscarriage (RR 1.23, 95% CI 0.72 to 2.10) or need for surgical evacuation (RR 0.62, 95% CI 0.17 to 2.26).

Nine studies (involving 1766 women) compared misoprostol (oral or vaginal or in combination of both route) with surgical evacuation. The success rate was high in both the methods but no statistically significant difference was observed (RR 0.96, 95% CI 0.92 - 1.00,). There were fewer surgical evacuations with misoprostol (average RR 0.07, 95% CI 0.03 - 0.18). Long-term follow up data was available from one study that found no difference in subsequent fertility among the three approaches.

A randomized trial of surgical, medical and expectant management of first trimester spontaneous miscarriage (50).

In 2005, Shelly JM et al conducted a randomized control trial to compare the effectiveness of medical management in women with incomplete or inevitable miscarriage with surgical or expectant management. The primary outcome was the effectiveness of medical

management i.e. vaginal misoprostol and expectant management relative to surgical evacuation, assessed at 10-14 days and 8 weeks after recruitment. They also assessed infection, pain, bleeding, and anxiety, and depression, physical and emotional recovery. Analysis was done to assess by intention-to-treat. Effectiveness was lower for medical (80.0%) and expectant (78.6%) than for surgical management (100.0%) at 8 weeks. There were two women with diagnosed infection in the medical management group. Bleeding lasted longer in the expectant group than in the surgical group. There were no significant differences in physical recovery, pain, anxiety or depression among the groups. 54.6%, 42.9% and 57.1% of the surgical, medical and expectant groups respectively had opted for the same treatment again.

Guidelines for medical method of pregnancy termination

American College of Obstetrics and Gynaecology (ACOG) (51)

For women with less than 12 week

- Incomplete pregnancy loss and the size of the uterus less than 12 weeks in size: Tab misoprostol 600 µg orally or 400 µg sublingually (52).
- Delayed pregnancy losses: Tab misoprostol 800 µg vaginally or 600 µg sublingually.
- Repeat doses can be used every 3 hours for up to three total doses (52).
- Different dosing regimen were studied and shown that, 800 µg, misoprostol produces the highest expulsion rate and additional third doses has minimal added benefit (53).

For women with gestation age of 7 to 17 weeks,

- 800-µg vaginal misoprostol regimen resulted in an 80% success rate within 3 days of treatment (37).
- There is similar efficacy among all modes of administration, although gastrointestinal (GI) side effects (nausea, diarrhea) are more common with oral misoprostol than sublingually (41).
- In multiple-dose regimens, i.e. every 3 to 4 hourly results in more GI side effects and 6- to 12-hour spacing is tolerable. The optimal dosing schedule should be determined by the route of administration. Ultimately, patient preference should be taken in consideration for the optimal route of administration because the efficacy of each approach is similar (54).

World Health Organization (WHO)

The WHO recommendation for medical method of termination of pregnancy is mifepristone (55).

Table 3: WHO guideline for medical management

Gestational age	**Recommendation**	**Dose and regimen**
Up to 9 weeks	Mifepristone followed by misoprostol	Mifepristone 200 mg orally Misoprostol 800 mcg after 1-2days (Vaginal, buccal or sublingual) or 400 mcg orally. • Up to 7 weeks (49 days) misoprostol may be used by vaginal/buccal/sublingual/ oral routes. • After 7 weeks of gestation, oral administration of misoprostol should not be used. • Up to 9 weeks (63 days) misoprostol can be administered by vaginal / buccal / sublingual routes.
9-12 week	Oral mifepristone followed by misoprostol	Mifepristone 200 mg orally Misoprostol 800 micrograms vaginally 36-48 hours after that. • Repeat misoprostol 400 mcg vaginally or sublingually, every 3 hours up to four further doses, till expulsion of the products of conception

Gestational age	Recommendation	Dose and regimen
Over 12 weeks	Oral mifepristone followed 36--48 hours by misoprostol.	At 12-24 weeks: • Mifepristone 200 mg orally • Misoprostol 800 mcg vaginally or 400 mcg orally. • Repeat misoprostol 400 mcg, either vaginally or sublingually, every 3 hours up to four further doses.

Table 4: Guideline in the region where Mifepristone is not available or not affordable

Gestational age	**Doses and regimen**
Up to 12 weeks (84 days)	• Misoprostol 800 mcg vaginal or sublingual routes. • Up to three repeat doses at intervals of at least 3 hours, but not beyond 12 hours.
Beyond 12 weeks (84 days)	Up to 24 week • Misoprostol 400 mcg vaginal or sublingual • Repeat every 3 hours for up to five dose Beyond 24 weeks: • Dose of misoprostol should be reduced, due to the greater sensitivity of the uterus to prostaglandins.

RCOG recommendation (56)

Medical abortion regimens using 200 mg oral mifepristone and misoprostol are effective and appropriate at any gestation. (Level B evidence)

Medical abortion at ≤ 63 days of gestation (Level B evidence)

- At ≤ 63 days of gestation, mifepristone 200mg orally followed by 24-48 hours later by misoprostol 800 micrograms given by the vaginal, buccal or sublingual route.
- At ≥ 49 days of gestation, 200 mg oral mifepristone followed 24-48 hours later by 400 micrograms of oral misoprostol.

- For women at 50-63 days of gestation, if abortion has not occurred 4 hours after administration of misoprostol, a second dose of misoprostol 400 micrograms may be administered vaginally or orally**.**

Medical abortion at 9-13 week of gestation (Level A evidence)

- Mifepristone 200 mg orally followed by 36-48 hours later by misoprostol 800micrograms vaginally. A maximum of four further doses of misoprostol 400 micrograms may be administered at 3-hourly interval, vaginally or orally.

Medical abortion at 13-24 weeks of gestation (Level A Evidence)

- Mifepristone 200 mg orally, followed by 36-48 hours later by misoprostol 800 mcg vaginally, then misoprostol 400 mcg orally or vaginally, 3-hourly, to a maximum of four further doses.
- If abortion does not occur, mifepristone can be repeated 3 hours after the last dose of misoprostol and 12 hours later misoprostol may be recommended.

NICE guideline (57).

- Mifepristone should not be offered as a treatment for missed or incomplete miscarriage.
- For the medical treatment of missed abortion or incomplete miscarriage offer misoprostol vaginally. If women prefer orally, it is an acceptable alternative.
- Use a single dose of 800 mcg of misoprostol for women with a missed miscarriage.

- The women should be advised to contact her healthcare professional, if bleeding has not started 24 hours after treatment, to determine ongoing individualized care.
- Use a single dose of 600 mcg of misoprostol for women with incomplete miscarriage. (Alternately, 800 mcg can be used for both missed and incomplete miscarriage).

Complication of first trimester pregnancy termination

The development of complication after pregnancy termination depends on method used, gestational age at termination, patient profile and clinician skill and experience (58,59). Major complications are readmission in hospital, sepsis, surgical intervention and blood transfusion. Recent evidence confirms that the absolute risk of complications following termination of pregnancy is low. A Canadian retrospective cohort study of 83,469 women with termination reported 571 (0.7%) women had immediate complications (58).

The complication can be early occurring within 6 hour of intervention like hemorrhage, uterine perforation, hematoma and maternal mortality or can be delayed developing after 6 hour of intervention like infection, retained product of conception and late sequel like intrauterine adhesion affecting the future fertility (60).

Early complication:

MVA done in the outpatient setting has less risk of maternal morbidity and mortality than done in the hospital setting. The immediate complication includes hemorrhage, cervical

laceration, and uterine perforation. The rate of complication was 0.06% in a retrospective study in New York Planned Parenthood.

Delayed complication

Delayed complications after MVA occur after 72 hour of procedure and it affects 1% of the women. Complication are fever, infection, hemorrhage and retained product of conception. The risk of post-abortal endometritis is 5-20% if antibiotics are not used. Use of prophylactic antibiotics reduces this risk to half (61–63).The risk of retained product of conception is a rare complication and present as isolated endometritis or endometritis with RPOC. Symptoms are fever, enlarged and tender uterus, and lower abdominal pain with increased bleeding per vagina. Ultrasound is used to differentiate between isolated endometritis or endometritis with RPOC as it is difficult to differentiate clinically.

Retained Product of conception (RPOC):

It affects 1% of pregnant women with early pregnancy loss and more common with first trimester pregnancy loss (64). The reported incidence depends on the method used, the symptom at follow up and the duration of follow up. Residual trophoblastic tissue can lead to one of the deadly complication as intrauterine adhesion affecting the future fertility of women. Intrauterine adhesion is more common after surgical method of termination and in second trimester loss (65). Hence, early diagnosis of retained trophoblastic tissue is crucial. It may clinically presents as enlarged, soft tender uterus with dilated cervical os and bleeding per vagina evident on speculum examination. On ultrasonography the endometrial cavity have hyper echogenic, hypo echogenic, or mixed echogenic space occupying pattern

with varying endometrial thickness. This nonspecific sonographic feature could be either retained trophoblastic tissue or just retained blood clots. Hence, finding a standard sonographic feature may obviate an unnecessary uterine exploration. The diagnostic accuracy for the retained product is better with combined clinical and ultrasound feature than the either clinical or sonography alone.

Spectrum of Sonographic appearance after first trimester abortion.

Retained product of conception is well known complication after spontaneous or induced abortion and diagnosed based on sonographic appearance of intrauterine endometrial contents. The appearance of the uterine cavity within the initial hours after abortion are described in few studies (66–68).

Bar-Hava et al (2001) had prospectively followed 74 women with endovaginal ultrasound after different type of abortion who underwent surgical evacuation at 1 week and repeated at 6 weeks. The aim of the study was to define the acceptable range of endometrial thickness and normal distribution of endometrial content to prevent unnecessary intervention. Sonographic finding was divided into 3 pattern depending on the appearance of intrauterine content, and anteroposterior thickness.

Pattern A: Thin, regular midline stripe, less than 7mm thick.

Pattern B: Thick, hyperechoic midline stripe, 7-19 mm thick.

Pattern C: Midline stripe, 20 mm or thicker, or very irregular echogenicity at least 14 mm thick.

On sonography, intrauterine contents were thicker and more irregular when patients were examined within first 48 hours as compared to those examined later. The echogenicity gradually decreased overtime and became hypoechoic. Seventy-seven percent of examination showed considerable amount of intrauterine content with varying echogenicity (anteroposterior thickness range, 7-61mm). All women with excessive intrauterine content followed after 6-8 week showed empty uterine cavity. Therefore, concluded that thick heterogeneous endometrium is an expected finding after first trimester abortion within the week. Hence, clinician should be familial with normal appearance and thickness of endometrium to avoid unnecessary evacuation. (68)

J. L. Alcazar et al in 1998 had prospectively evaluated 45 women with vaginal bleeding post abortion and postpartum with color Doppler velocimetry imaging to diagnose retained trophoblastic tissue. Pulsed wave Doppler was used to assess blood flow impedance to calculate resistance index. The presence of abundant blood flow with a lower resistance index less than 0.45 was suspected as residual trophoblastic tissue. Women with suspicious Doppler finding underwent dilation and curettage and histopathological examination confirmed residual trophoblastic tissue (93.3%). This study suggested that transvaginal ultra sound (TVS) with pulsed wave Doppler could be useful for detection of retained trophoblastic tissue. (69)

Cowett et al had retrospectively reviewed the cohort of women in 2001-2003 who underwent medical abortion and determined the ultra-sonographic parameter for the need for further dose of misoprostol / mifepristone or surgical evacuation (70). Six hundred

eighty-four women received single dose of mifepristone 200mg and then after 24-72 hour, 4-misoprostol 200-mcg tablet self-administered intravaginal. Women were followed after 7-10 days. At follow up visit, women were asked the history of passage of product and vaginal ultrasonography was done. Absence of gestational sac confirmed the expulsion and their presence was denoted as treatment failure. In the treatment failure group, additional misoprostol was given and followed for next 7-10 days. Surgical evacuation was considered only if there was continuous bleeding per vagina or incomplete expulsion after 3 weeks. The post procedure ultrasonography was done to evaluate the measurement of endometrial thickness, presence of fluid interface, complex echo or persistent gestational sac. The result is showed in Table 5 and Table 6.

Table 5: Endometrial stripe of All Patients, Successes and Failures

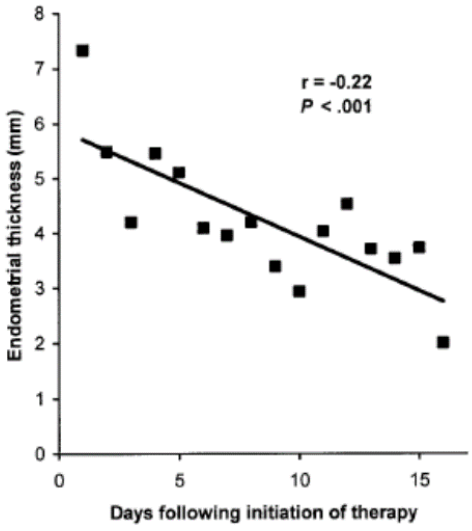
	All Patients (n=437)	Successes (n=419)	Failures (n=18)	P value
Endometrial stripe (mm)	4.10 ± 1.80 (0.67-13.4)	4.01 ± 1.80 (0.67-13.4)	6.15 ± 1.95 (3.35-10.0)	< 0.001

Table 6: Ultrasound finding of All Patients, Successes and Failures

Ultrasound finding	All Patients (n=516)	Successes (n=497)	Failures (n=19)	Odd ratio	95% CI
Complex echoes	91 (17.6)	84 (16.9)	7 (36.8)	2.87	1.10,7.50
Fluid interference	35 (6.80)	31 (6.20)	4 (21.1)	4.01	1.26,12.8
Gestational sac	6 (1.20)	0 (0.0)	6 (1000	∞	

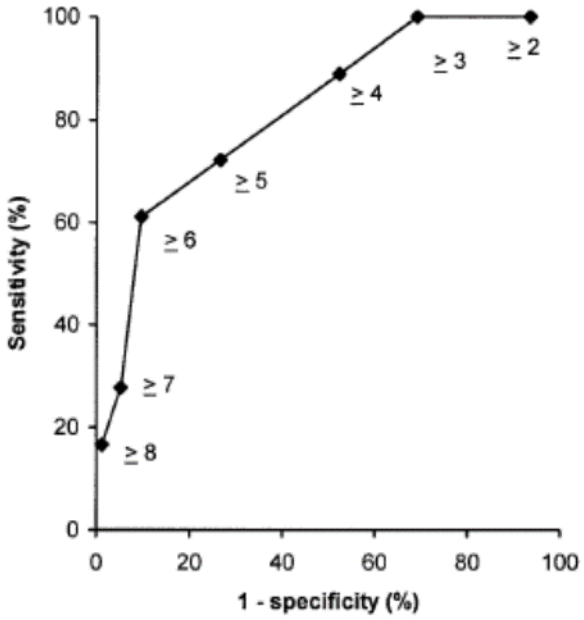
It was concluded that the relationship of endometrial thickness to the interval to initiation of therapy was inversely related. (r =-0.22; P <0.001). (Figure: 2)

Figure 2: Relationship between endometrial thickness and interval of initiation of therapy:



They attempted to find endometrial thickness measurements that could predict a successful medical abortion. They plotted ROC curve and demonstrated that there was no acceptable measurement at which false positive and false negative rate can be minimized.

Figure: 3 ROC for the cutoff point of endometrial thickness.



Matthew F et al (2004) had randomized 653 women with early pregnancy loss into misoprostol group (491) and D&C group (161). Transvaginal ultrasonography was planned on day 2 and day 14 after misoprostol treatment and 14 days after D&C. The primary objective of the study was to compare endometrial thickness after misoprostol or D&C and to assess the predictive value of endometrial thickness for subsequent D&C after misoprostol treatment. The mean endometrial thickness at 14 days after treatment varied widely for women in both groups. The mean endometrial thickness was 9.0 mm for the misoprostol group and 6.9 mm for the D&C, (difference 2.1 mm, 95% CI 1.0 to 3.2, P <0.001). Women requiring D&C after successful expulsion had significantly greater endometrial thickness than those who did not at 2 days (mean difference 5.2 mm, 95% CI 1.6–8.8) and 14 days (mean difference 5.5 mm, 95% CI 2.3– 8.8) after misoprostol. Study

showed that the difference in endometrial thickness between misoprostol treatment and D&C for early pregnancy failure is not clinically significant. Endometrial thickness is not a useful predictor of subsequent surgical intervention after successful expulsion of the gestational sac after misoprostol for early pregnancy failure (71).

In 2004, S.W. Leung et al randomized 46 women with sonographic feature WITH suspected significant retained product of conception after misoprostol treatment into conservative management and surgical evacuation. They defined the sonographic finding as "empty uterus" if homogenous intrauterine dimension is less than $11cm^2$ in combined transverse and sagittal plane. Finding beyond this was denoted as suspicious of RPOC (72).

Table: 7 Outcome of two group of women

	Conservative groups(n=24)	Surgical evacuation groups (n=22)	P value
Without short-term complications	15	21	0.02
With short term complication needing repeat hospital readmission	9	0	

On interim analysis, a significantly higher complication rate was detected in the group randomized to conservative management. Therefore, trial was prematurely terminated.

Debby et al (2006) had conducted a randomized study to assess the incidence of RPOC in relation to transvaginal ultrasound performed after first trimester abortion. Eight hundred

and nine women after uterine evacuation randomized to undergo transvaginal ultrasonography in study group and no transvaginal ultrasonography in control group. The endometrial thickness immediately after surgical curettage was ≥ 8mm. Women were followed after 5-8 days by TVS.

Table: 8 Outcome between the group.

Complication	Study group (n=404)	Control group (n=405)	P value
Vaginal bleeding	1(0.5)	7 (1.7)	NS
Endometritis	1(0.2)	6 (1.5)	NS
Uterine perforation	0	1(0.2)	NS
RPOC	3(0.7)	15(3.7)	<0.05
Total	6 (1.5)	29(7.1)	<0.05

They concluded that total complication rate and the risk of RPOC could be reduced by performing the transvaginal ultrasonography after surgical evacuation. Women with endometrial thickness ≥ 8mm at the end of evacuation required re-evacuation (5).

Sawyer et al (2006) looked for endometrial volume to predict the presence of RPOC in a prospective observational study. 109 women with suspected retained product of conception presented with vaginal bleeding >7 days after medical or surgical method of termination of pregnancy, underwent transvaginal ultrasonography before repeat surgical evacuation. The surgical specimen was sent for histological examination. The measurement of endometrial thickness taken in the longitudinal view in such a way that include the

maximum anteroposterior diameter of the uterine cavity at the site of suspected RPOC. The suspected RPOC were measured in three perpendicular planes and the volume was calculated by using formula of ovoid volume (D1 × D2 × D3 × 0.532). They concluded with logistic regression analyses that at cut off level of >1ml, the diagnosis of incomplete abortion could be made with sensitivity of 89% (95% CI 82-94%), specificity of 32% (95% CI 15-54%), and positive predictive value of 88% (95% CI 81-93%) (6).

Abbasi et al (2008) in a retrospective study showed that presence of hyperechoic material on ultrasound is highly predictive of RPOC with the sensitivity of 78% and specificity of 100%. However, the exact endometrial thickness above which the risk of RPOC could be predicted was not studied (73).

In 2008, Debby et al had retrospectively studied the medical record of 599 women who underwent uterine evacuation by various method and followed at 5-8 days with ultrasound. The aim of the study was to describe the natural pattern of different sonographic finding of uterine cavity after first trimester abortion to reduce the unnecessary intervention. The thickness of endometrial lining was measured in anteroposterior diameter of the uterine cavity in longitudinal view. The endometrial findings were grouped into different four group as:

Group 1: Normal endometrial content, (when endometrium was regular with echogenicity similar to normal endometrium “empty cavity”).

Patient with abnormal endometrial content subdivided into:

Group 2: Hyperechoic pattern

Group 3: Mixed echogenic pattern

Group 4: Hyper-echogenic pattern

Women with abnormal sonographic pattern at first examination followed up weekly until the endometrium became normal. Depending on the symptoms like presence or absence of abdominal pain, and or fever, vaginal bleeding, the abnormal sonographic pattern was divided in to normal or abnormal. They concluded that hyperechoic endometrial content stayed longer than the other endometrial content finding (median 12 days' verses 8 days with P value <0.005). They also concluded that the thickness of the abnormal endometrial content in the asymptomatic patients gradually decreased to normal around the time of menstruation. There was no such change in the symptomatic patients, and those needed surgical intervention eventually (74).

In a retrospective study by Kamaya et al color Doppler study was studied to characterize the endometrial vascularity for the diagnosis of RPOC. The radiology database was searched between 2005 and 2008 of women referred for suspected RPOC for pelvic sonography. A total of 269 patients were identified and 35 of them had confirmed histological diagnosis. 28 out of 35 women with RPOC had positive color Doppler signal. The presence of a color Doppler signal and the amount of endometrial vascularity were subdivided into different type:

Type 0: Avascular color Doppler appearance with undetectable vascularity in the endometrium.

Type 1: Minimal vascularity with some detectable color doppler flow in the

endometrium but less than in the myometrium in the same image section.

Type 2: Moderate vascularity with vascularity equal to or near equal to that in the myometrium in the same image section

Type 3: Marked vascularity was defined as marked endometrial vascularity greater than that in the myometrium in the same image section.

The analysis of data from 28 women with RPOC shown that, 5 (18%) were avascular (type 0); 6 (21%) had minimal vascularity (type 1); 12 women (43%) had moderate vascularity (type 2); and 5 (18%) had marked vascularity (type 3). Five (45%) of the women with type 0 vascularity had RPOC; 6 (86%) of those with type 1 had RPOC; and 17 (100%) of those with types 2 and 3 had RPOC. Endometrial vascularity highly correlated with RPOC, whereas absence of vascularity could be seen in both avascular RPOC and intrauterine clots (75).

Igal Wolman et al (2009) in one retrospective chart review showed that the combined clinical and TVS approach enable to diagnose RPOC with greater accuracy with sensitivity of 94% and specificity 98% (76).

Table: 9 Spectrum of sonographic finding of the intra uterine content after early pregnancy (68–71,73,75,77,78)

Author Journal	**Type of study/Participants**	**Primary outcome**	**Result**
J Ultrasound Med 2001 *Bar –Hava et al* (68)	Prospective observational study (n=57)	Characterize the sonographic appearance of the uterine cavity after uncomplicated 1st trimester abortion	After a week echogenicity was present in 77% women (AP thickness range, 7-61 mm) compared with 17% had thin endometrial lining.
Ultrasound obstetrics Gynecology 1998 *Alcazar et al* (69)	Prospective observational study (n=40)	To evaluate transvaginal color velocity imaging and pulsed Doppler Ultrasonography could improve the diagnostic accuracy of transvaginal ultrasound alone.	• Mean endometrial thickness higher with residual tissue (U value 64.5 p =0.025) • Mean lowest RI with histologically proven residual tissue was significantly low (U value 16.5, p=0.0001) • Sensitivity, Specificity, PPV and NPV with abundant blood flow at lowest RI of < 0.45 were 93.3%,96%,93.3%and 96% respectively
Ultrasound Obstetrics Gynecology 2007 *Sawyer et al* (6)	Prospective observational study (n=109)	Identify ultrasound measurements that are the best predictors of the presence of RPOC in women with clinical diagnosis of incomplete miscarriage.	No identifiable cut-off for endometrial thickness or volume that could be used to differentiate between retained products of conception and decidua.

Author Journal	Type of study/Participants	Primary outcome	Result
ACOG 2004 *Cowett et al* (23)	Retrospective study (n=525)	Determine ultrasound parameters associated with the need for clinical intervention after mifepristone and misoprostol termination of pregnancy	• Mean endometrial thickness was 4.10 ± 1.80 mm (range 0.67–13.4 mm). • Indirect correlation between endometrial thickness and number of days after initiation of therapy (r = –0.22; P < .001). • Difference between endometrial thickness of treatment failure and successful group (6.15 ± 1.95 mm; P < .001).
J. Ultrasound Med 2009 *Kamaya et al.* (75)	Retrospective study (n=269)	To characterize color Doppler imaging features of RPOC with gray scale correlation.	• Women with RPOC color Doppler were avascular, minimal, moderate and marked vascularity were 18%, 21%, 43 %, and 18% respectively. • An echogenic mass had PPV 80% but low sensitivity (29%) for RPOC

Author Journal	**Type of study/Participants**	**Primary outcome**	**Result**
ACOG 2008 *Mathew F.et al* (71)	Randomized trial (n=491)	Compare endometrial thickness after misoprostol and D & C for early pregnancy failure. Assess the predictive value of endometrial thickness for subsequent D & C after misoprostol treatment	• Mean endometrial thickness for misoprostol and D &C group was 9mm and 6.9 mm respectively (difference 2.1 mm, 95% CI 1.0 to 3.2). • Significant greater endometrial thickness in women requiring D&C than who did not after successful expulsion at 2 days (mean difference 5.2 mm, 95% CI 1.6 to 8.8) and 14 days (mean difference 5.5 mm, 95% CI 2.3–8.8). • The areas under the ROC curves for endometrial thickness at 2 and 14 days were 0.71 and 0.73, respectively. • The cutoff values of endometrial thickness for predicting need for D&C had a positive predictive value of 40% or less.

Author Journal	**Type of study/Participants**	**Primary outcome**	**Result**
Ultrasound Obstetrics gynecology 2008 *Abbasi et al* (73)	Retrospective study (n=91)	Assess the role of clinical and ultrasound findings as predictors of RPOC in women with a suspicion of incomplete miscarriage.	• Vaginal bleeding was more frequent with RPOC (P < 0.001). Sensitivity, Specificity, PPV and NPV of 93%, 50%, 74% and 82% respectively. • Lower abdominal pain was a more frequent symptom (P = 0.019). • Presence of hyper echogenicity had a sensitivity, specificity, PPV and NPV of 78%,100%,100% and 75%, respectively, in predicting RPOC • There was no significant difference in endometrial thickness between the two groups.
Ultrasound Obstetrics Gynecology 2008 *Debby A.et al* (78)	Retrospective study (n=599)	Characterize the sonographic appearance of the uterine cavity after 1st trimester uterine evacuation in an attempt to reduce the number of unnecessary surgical interventions.	• Need longer time for normalization in hyperechoic (median, 12 days) compared with hypo or mixed echogenicity (8 and 9 days, respectively, P < 0.0001). • Longer duration of vaginal bleeding in women with hyperechoic material than women with hypo or mixed echogenicity (9, 7 and 5 days, respectively, P < 0.0001).

Misoprostol regimen is currently the recommended medical management of early pregnancy failure. It is speculated that 29% of women will have incomplete evacuation by day 3 of misoprostol and may need curettage (3). Clinical and sonologic feature that would help to decide on the need for curettage are still not well established and hence management is individualized (76). However, some studies have looked for clinical feature to predict successful treatment after misoprostol.

Mitchell D.et al had conducted a secondary analysis of the data from one multicenter trial that compared the medical and surgical method for early pregnancy failure to identify the potential predictors of success of medical management. Success with misoprostol was defined as complete abortion without the need for a vacuum aspiration within 30 days of treatment. Out of 491 women who received misoprostol in the trial, 485 women fulfilled the criteria for secondary analysis. Women included in the analysis were anembryonic gestation (36.5%), embryonic /fetal demise (57.5%) and incomplete/ inevitable abortion (6.0%). Multivariable analysis revealed that the presence of lower abdominal pain or vaginal bleeding within 24 hours, Rh negative blood type and null parity were predictive of overall success (79).

After misoprostol, patients who have active bleeding per vagina with open cervical os undergo surgical evacuation. Patients, who expel the sac or fleshy mass in toto and have minimal bleeding per vagina, are diagnosed as complete expulsion.However, the ultrasound findings that would predict the presence of incomplete evacuation are not well established. The ultrasound findings commonly used are, endometrial thickness, regularity

of the endometrial lining and the echogenicity of the content if any, and the decision for surgical evacuation or follow-up is made on an individual basis.

Currently the decision for curettage after medical management is taken on an individual basis, as there are no definite guidelines based on ultrasound findings suggestive of retained products. Misoprostol regimen is popularly used for termination of early pregnancy loss and this is the present standard of care currently followed in our institution. This regimen is used instead of recommended mifepristone, as mifepristone is costly and not easily available. Misoprostol is cheaper and more patient friendly. Hence, misoprostol is recommended in low resource settings by the WHO (55). The success rate for medical management is speculated to be 71% and 84% by day 3 and day 8 respectively (6).

In our institution, the dosing regimen recommended by the WHO is mostly followed (80). Misoprostol is administered vaginally following admission and patients are evaluated with history, clinical and ultrasound examination to ensure complete expulsion after administration of the recommended regimes. Women who have complete evacuation without prolonged period of excessive bleeding do not have an emergency curettage. However, after complete expulsion, most women have a scan and curettage may be done. Some clinicians do not perform curettage and choose to follow-up women with or without repeat doses of misoprostol while others perform curettage for thickened endometrium. Since there is very little information on the ideal method of management several studies have looked at ultrasound findings that could predict the presence of retained products of conception. The findings looked at the thickness of endometrium varying from 8 to 30 mm,

the echogenicity of the endometrial contents and volume of the endometrial content but none of these studies could definitely state findings that could conclusively diagnose incomplete expulsion mandating the need for curettage. Wolman and Abassi S. et al (73,76) concluded that a combination of clinical and ultrasound findings is more helpful in diagnosis of incomplete abortion than ultrasound alone.

In this study, we observed the patients who have had termination for an early pregnancy failure by medical methods. Their clinical symptoms and scan findings after medical termination were noted. Following misoprostol, the decision for curettage, repeat dosing or discharge was made by the primary care giver. These patients were followed up for a duration of 6 weeks and enquired regarding readmission for curettage or any other complications like pelvic, abdominal pain or fever. Comparators were women who had curettage and women who had curettage or had repeat doses of misoprostol.

METHODS AND MATERIALS

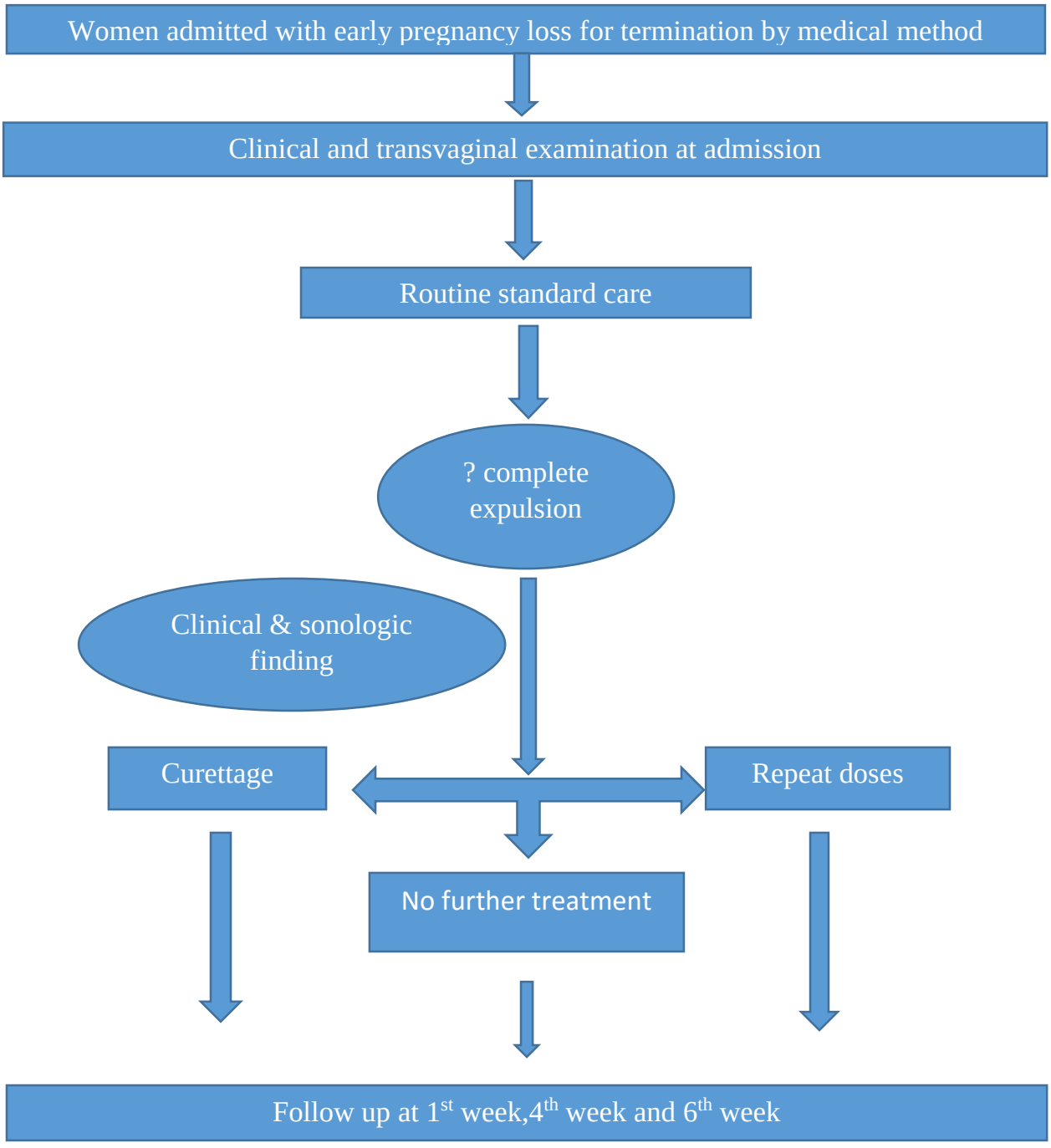
Study Design: It was a prospective observational study. The women who were admitted for termination after diagnosis of early pregnancy failure in first trimester were studied.

Study period: November 2015 to July 2016

Setting: All women presented to labour room, outpatient department, maternity wards of Christian Medical College, Vellore.

Methodology: Women, who were admitted for termination by medical method after diagnosis of early pregnancy failure in first trimester, were enrolled into our study after informed consent. The routine management was continued. We followed the detail about the treatment given to the women during hospital stay. The details were recorded about dose regimen which was used for termination, number of doses administered. Details were also recorded about modality of treatment, whether medical or surgical, that is used if incomplete expulsion was suspected based on clinical and sonologic features. Total duration of hospital stays and any morbidity during that period were also recorded. Symptoms, sonologic and clinical findings prior to and after termination were also noted. We followed women by telephonic call at 1 week, 4 weeks and 6 weeks after discharge. We inquired about following symptoms: fever, persistent spotting, foul smelling vaginal discharge or pelvic pain. We followed them if they required further hospital admission or consultation to doctor and noted down the clinical and sonologic finding.

Figure: 4 The follow up plan for the study cohort



Sample size: Sample size was calculated as below

$N= (Z^2-\alpha)^2 p\ q/d^2$

$= (1.96)^2pq/d^2$

$=4pq/d^2$

Here,

p=the probability of incomplete evacuation (30%),

q=probability of complete evacuation (70%)

d=margin of error (4%)

Hence the sample size

$N = 4\times30\times70/4\times4$

N=560

Statistical methods: Categorical variables were summarized using counts and percentages. Quantitative variables were summarized using mean and standard deviation or median and range. Two sample t tests was used to compare means between the two groups and Chi square test was used to compare the proportions between the two study groups. For non-normal variables, Mann Whitney's U test was carried out. For all the analysis, 5% level of significance was considered significant.

Inclusion criteria: Women with early pregnancy loss with

a. GA < 14 weeks
b. Anembryonic pregnancy
c. Embryonic /Early fetal demise

Exclusion criteria:

a. Gestational age ≥ 14 weeks
b. Hemodynamically unstable patient or active bleeding or H/O passage of clots
c. History of prior intervention with either medical management or curettage prior to admission
d. Allergy to misoprostol
e. Patient with bleeding disorder or on anticoagulants
f. Evidence of sepsis

Primary Outcome:

a. Requirement of readmission or for further treatment.
b. Repeat curettage, excessive bleeding or passage of clots, fever, abdominal or pelvic pain, foul-smelling discharge

Outcomes: Data were obtained on follow up if admitted in CMC again. Phone call at one week, four weeks and six weeks were made. The clinical outcomes were obtained from the women and their clinical notes.

Predictors: Predictors, potential confounders and effect modifiers

- Clinical features prior to admission for termination
- Duration of bleeding or spotting
- Amount of bleeding
- Type of gestation – anembryonic or embryonic
- History of passage of tissue
- Gestational age at admission < 12wks and >12 wks.
- Regimen of Misoprostol used
- Number of doses of misoprostol used
- Induction to expulsion interval
- Clinical features prior to curettage or follow-up
    - Amount of bleeding or number of pads soaked
    - Cervical os open or closed
    - Duration of bleeding in hours
    - Abdominal pain
- Ultrasound features prior to curettage or follow-up
    - Endometrial thickness
    - Presence of echogenic material
    - Irregularity of endometrium – present or absent
- Seniority of person making the decision
- Seniority of person doing the curettage
- Reason for making the decision

- Previous history of PID in patient
- Previous history of DUB in patient
- Duration of hospital stay before discharge, after termination in hours.

Bias: History, clinical examination and sonography techniques and interpretation of these finding could vary between examiners (Obstetrician), but the chance of inter observer variation were less. Principal investigator reviewed findings wherever feasible.

RESULT

During the study of nine-month period from November 2015 to July 2016, 170 women with early pregnancy loss were admitted for termination of pregnancy. Fifty-eight women excluded from the study population. 41 of them had incomplete abortion admitted with active bleeding per vagina or history of passage of product before admission, 12 women pregnancy were terminated due to anomalous fetuses, three for maternal condition (two with nonfunctional chronic kidney disease and one with diagnosed breast cancer planned for chemotherapy), one mother was on anticoagulant and one had septic abortion. Hundred and twelve women met the inclusion criteria for the study. Out of the eligible study population twelve mother refused consent. Hence, 100 women followed up in the study.

Figure 5: Flow chart showing eligible study population.

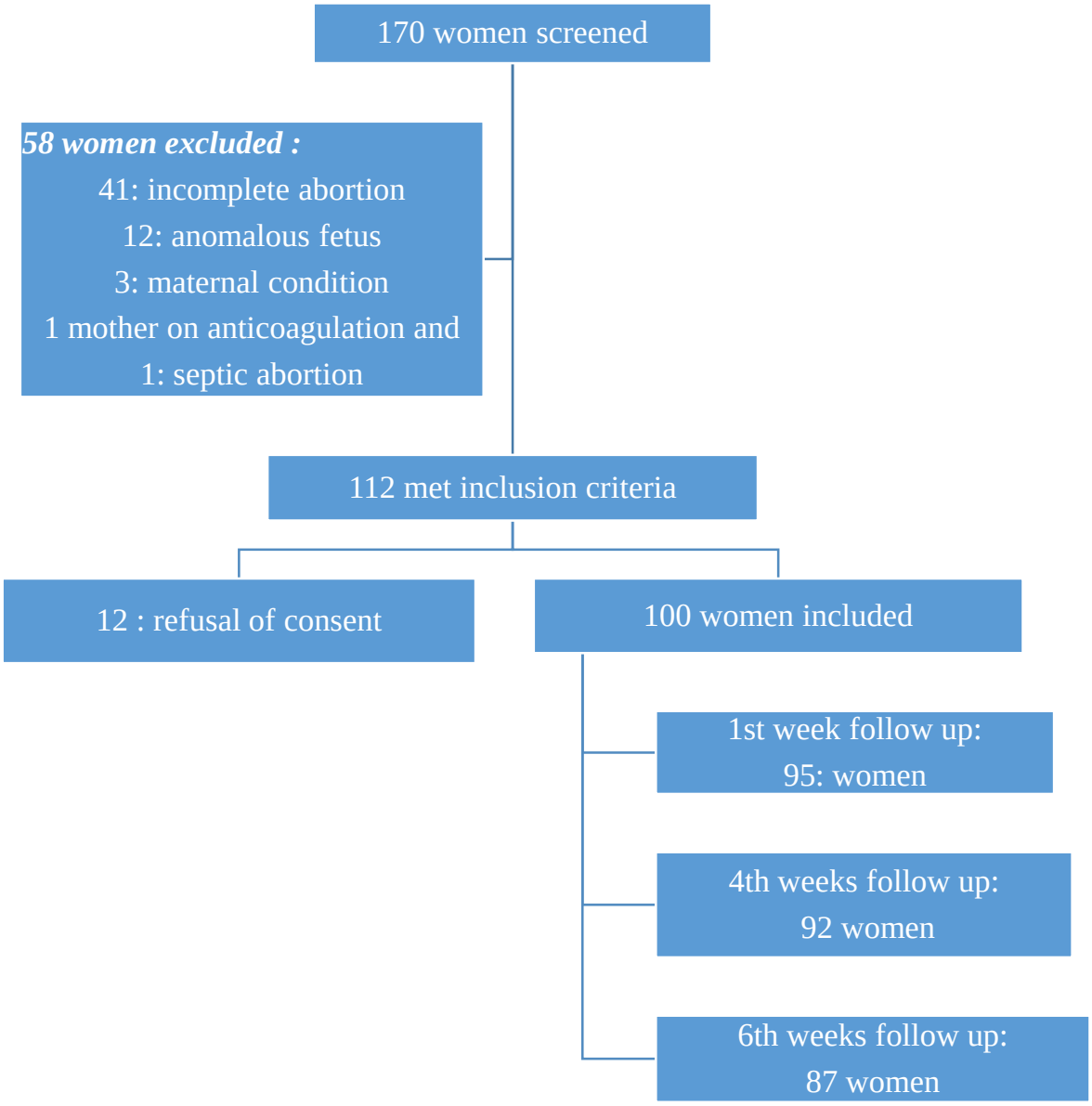


Table 10: Demographic characteristics of the study cohorts:

Variables	Mean (percentage %)
Age (years)	26.44(4.91)
BMI (kg/m^2)	24.71(6.20)
Height (cm)	155.01(5.86)
Weight (Kg)	59.4 (15.26)

The mean age, BMI, height and weight of the study population were 26.4 years, 24.71 kg/m^2, 155 cm and 59.4 kg respectively.

Table 11: Obstetrics score:

Obstetrics score	Number (Percentage %)
Obstetrics score (Gravida) • Primi • Multi	 48 (48) 52 (52)
Obstetrics score (Parity) • Null parity • Primi parity • Multiparty	 58 (58.6) 32 (32.3) 9 (9.1)
Living • No • One or more	 66 (66) 34(34)

Among the women included in the study, 48 were primi gravida and 52 were multigravida. The total numbers of nulliparous, primiparous and multiparous women were 58, 32 and 9 respectively. Sixty-six of them had no living issue, 34 had one or more living issue.

Table 12: Blood group distribution of study population

Blood group	Frequency (percentage %)
A	16 (16.16)
B	30 (30.3)
AB	9 (9)
O	40 (40.4)
Rh Negative	4 (4.04)

The most common blood group noted was O followed by B, A and AB.

Table 13: Previous history

	Number (Percentage %)
Previous history of MTP	
None	72 (72)
Once	15 (15)
Twice	7 (7)
More than twice	6 (6)
Previous history of PID	2 (2)
Previous history of DUB	7 (7)

Among the included women, 72 women had no previous history of abortion, 15 had once, seven had twice and six had more than twice. Two of them had previous history of pelvic inflammatory disease and seven had previous history of dysfunctional uterine bleeding.

Table 14: Gestational age at diagnosis of early pregnancy loss:

GA at Diagnosis	Number (Percentage %)
Less than 12 weeks	87 (87)
12-14 weeks	13 (13)

In eighty- seven women, the missed abortion diagnosed before 12 weeks and in thirteen women between 12 to14 weeks.

Figure: 6

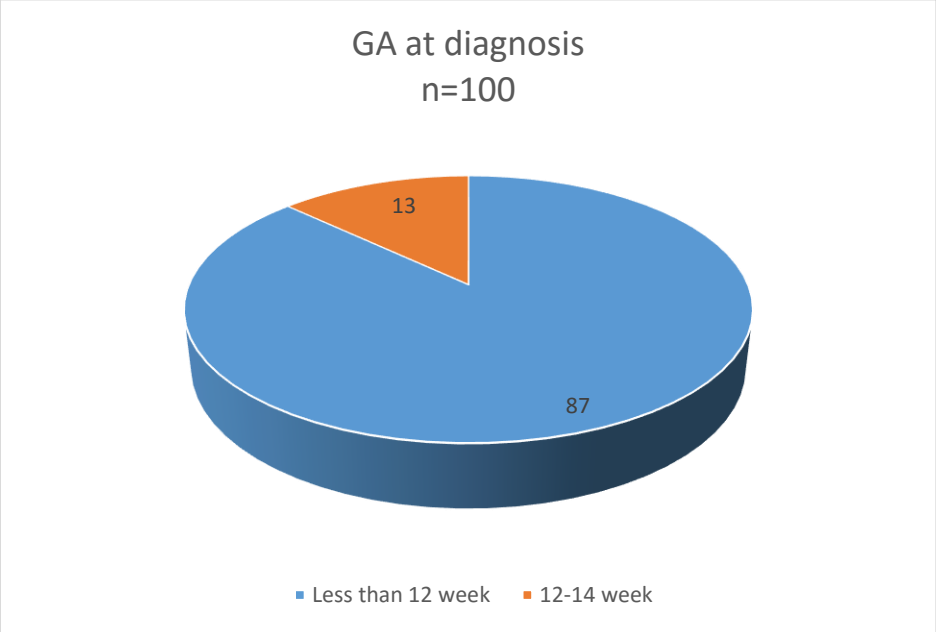
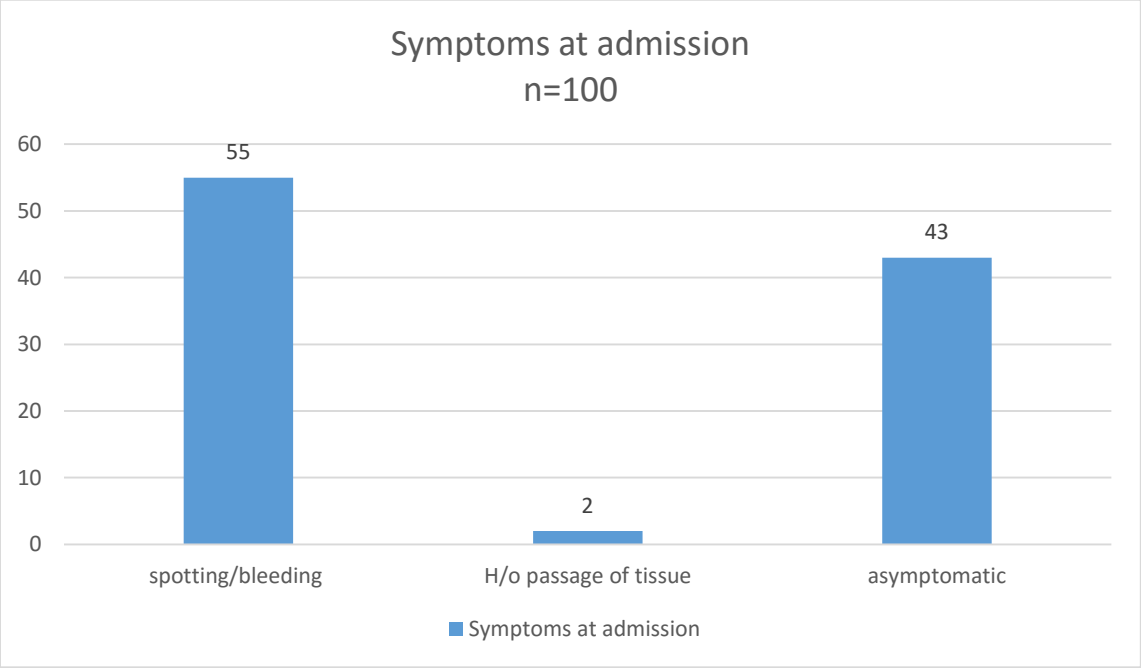


Table 15: Gestational age at the time of admission:

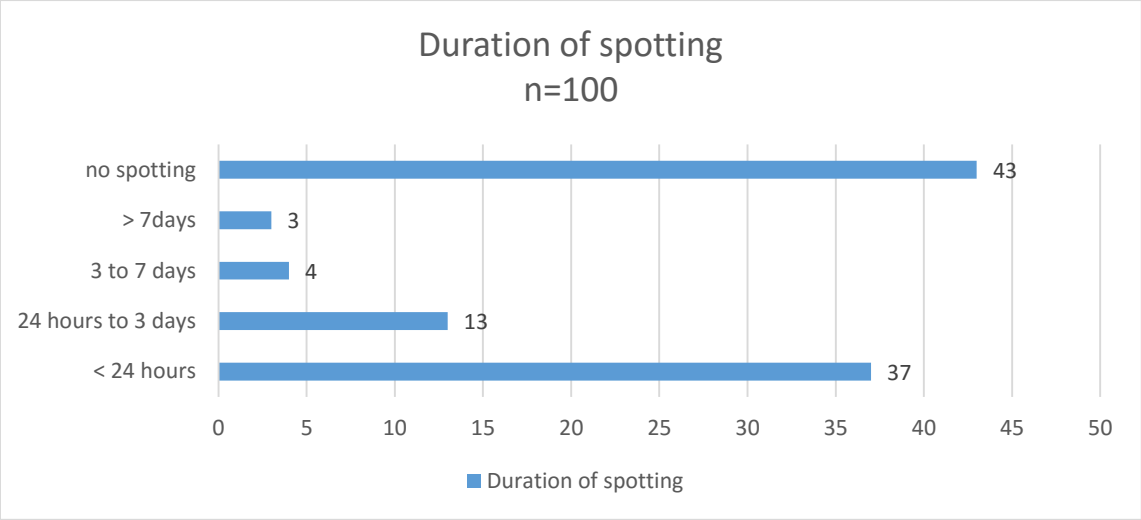
GA at admission	Number (Percentage %)
Less than 9 weeks	15 (15)
9-13 weeks	75 (75)
13-14 weeks	10 (10)

Figure: 7 Symptoms at the time of admission



Forty-three percentages of women were asymptomatic at admission. Fifty-five percentage women had spotting/bleeding and 2% had passed tissue.

Figure 8 Duration of spotting at the time of admission



Thirty-seven women had history of spotting for less than 24 hours, 13 had for 24 hours to 3 days, four had 3-7 days and three women had for more than 7 days.

Table 16: Different dose regimens of misoprostol used for termination of pregnancy

Regimen used	Number (percentage %)
800 mcg every 12 hourly	95 (95)
400mcg every 6 hourly	5 (50

Figure:9

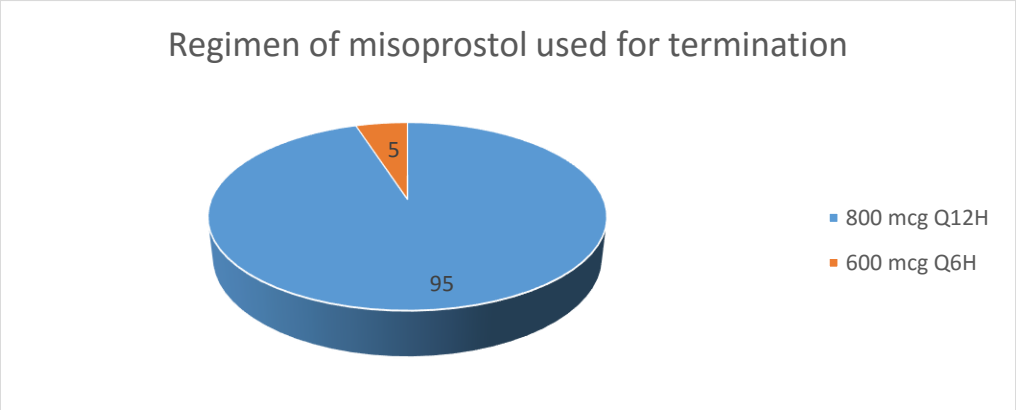


Table 17: Total numbers of misoprostol used

No of doses used	Frequency
1	15
2	28
3	53
More than 3	4

In majority of women, the total number of misoprostol used was 2 to 3 doses (28% and 53 % respectively)

Figure: 10: Total numbers of misoprostol used

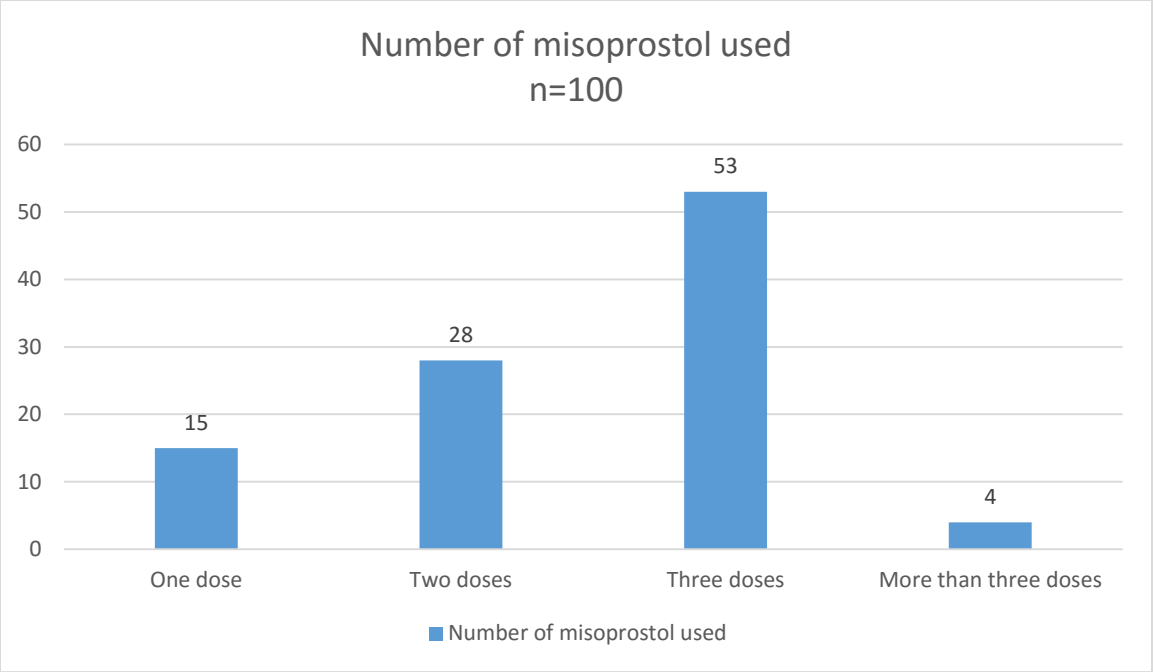
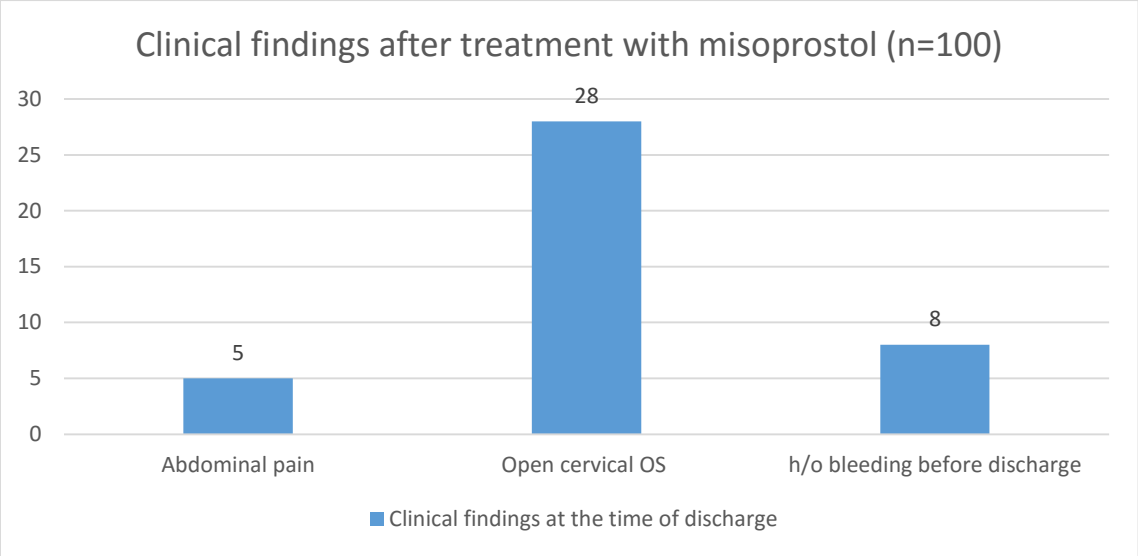


Table 18: Clinical finding after treatment with misoprostol in the study population

Clinical finding		Frequency
Abdominal pain	Yes	5
	No	95
Status of cervical os on vaginal examination	Open	28
	Closed	72
H/O spotting before discharge	Yes	8
	No	91

Figure: 11 Clinical finding after treatment with misoprostol in the study population



After treatment with misoprostol, if there was suspicion of incomplete expulsion ultrasound was done to confirm the diagnosis. The parameters observed in ultrasound were endometrial thickness, irregularity of the endometrial lining and echogenicity of the content. After treatment with misoprostol before discharge, ultrasounds were done in 83 women. The measurement of endometrial thickness was documented in 71 women and the irregularity of the endometrial lining and echogenicity were taken in 81 and 82 women respectively.

Ultrasound finding after treatment with misoprostol before discharge

Table 19: Endometrial thickness after treatment with Misoprostol

Endometrial thickness	Number (Percentage %) (n =71)
<5mm	7 (9.9)
5-7mm	13 (18.3)
8-12mm	28 (39.4)
13-15mm	5 (7.0)
16-25mm	15 (21.1)
26-30mm	2 (2.8)
>30mm	1(1.4)

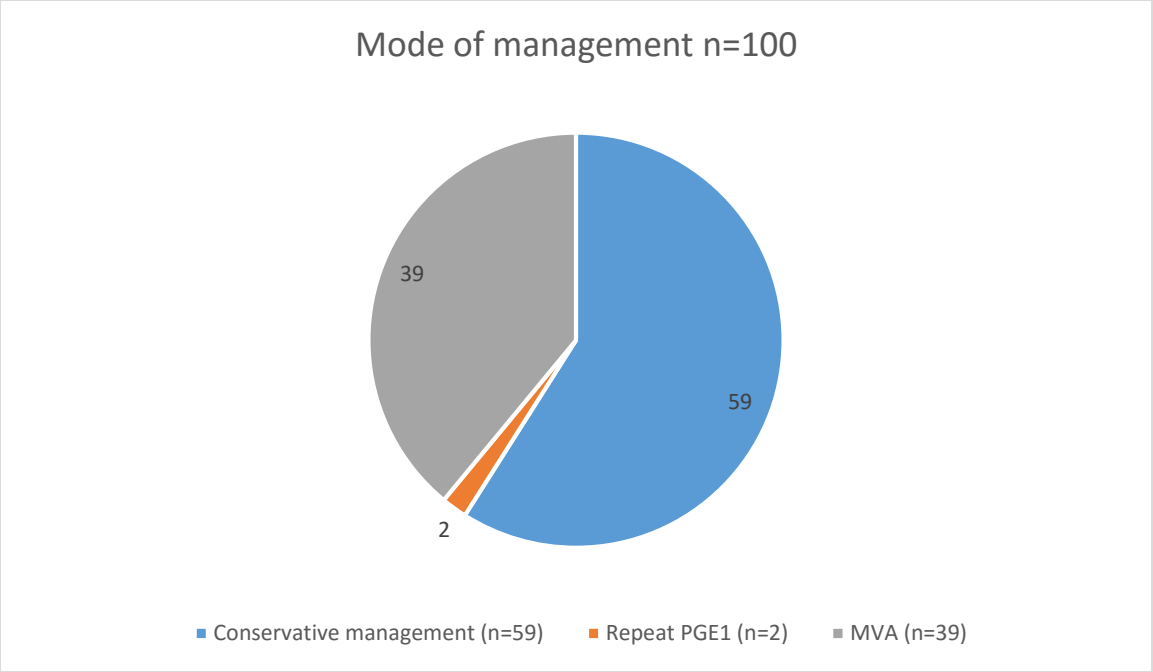
Table 20: Sonologic appearance after treatment with Misoprostol

Sonologic finding		Number (Percentage %)
Echogenicity of the content (n=82)	Yes	22(24.1)
	No	60(75.9)
Irregularity of the endometrial lining(n=81)	Yes	18(20.5)
	No	63(79.5)

Out of 100 women, 59 women were presumed to have complete expulsion and remaining 41 had incomplete expulsion clinically or sonologically. The criteria for the diagnosis of complete expulsion were either history suggesting of complete expulsion of the sac in toto or by sonologic examination by absence of gestational sac in the uterine cavity.

The treating physician had taken the decision for conservative management, repeat further doses of misoprostol, or treat with manual vacuum aspiration. Fifty-nine women had complete expulsion and required no further treatment. Out of 41 women with incomplete expulsion, two of them received repeat doses of Misoprostol and 39 underwent manual vacuum aspiration.

Figure: 12 Mode of management after the treatment with Misoprostol



The treating physician based on the ultrasound finding or symptom of persistent bleeding or by their clinical experience alone or in combination took the decision of either method

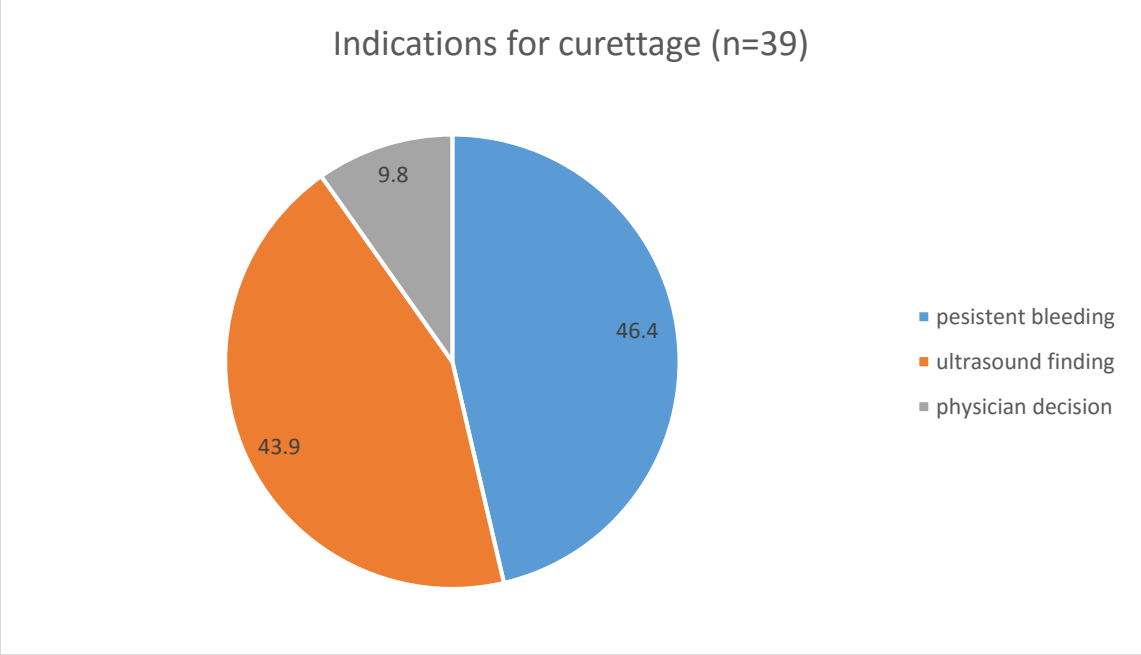
of management. Either junior consultant or senior registrar with good experience did MVA.

Table 21: Indication for curettage

Indication	Frequency (%)
Persistent bleeding	46.4
Ultrasound finding	43.9
Physician decision	9.8

The presence of persistent spotting and the ultrasound finding were the most common factor for the decision for curettage (26.4% and 43.9%) either alone or in combination. Rest were decided upon the physician according.

Figure: 13 Indication for curettage

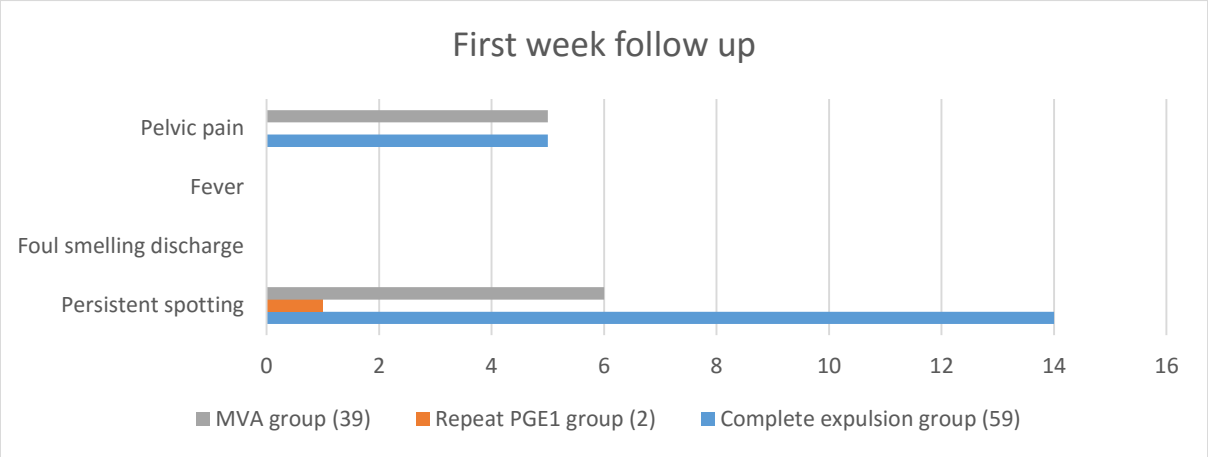


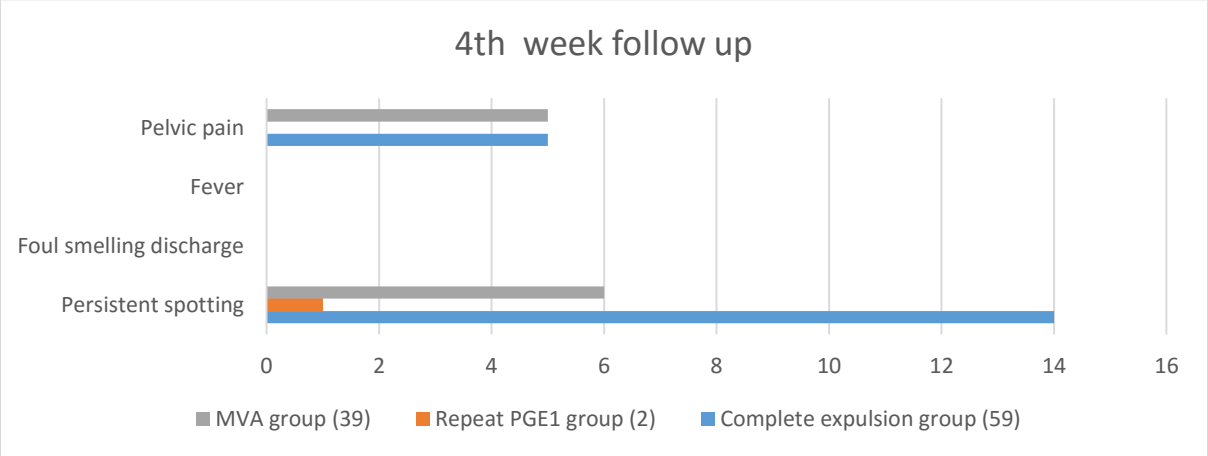
After discharge all the study participants were followed by telephonic call at the end of 1st week, 4th week and 6th week. Details were collected about the symptoms like persistent spotting per vagina, foul smelling vaginal discharge, fever or pelvic pain. Loss to follow up: five women were lost to follow up by first week, three by 4th week and another 5 by the end of 6th week.

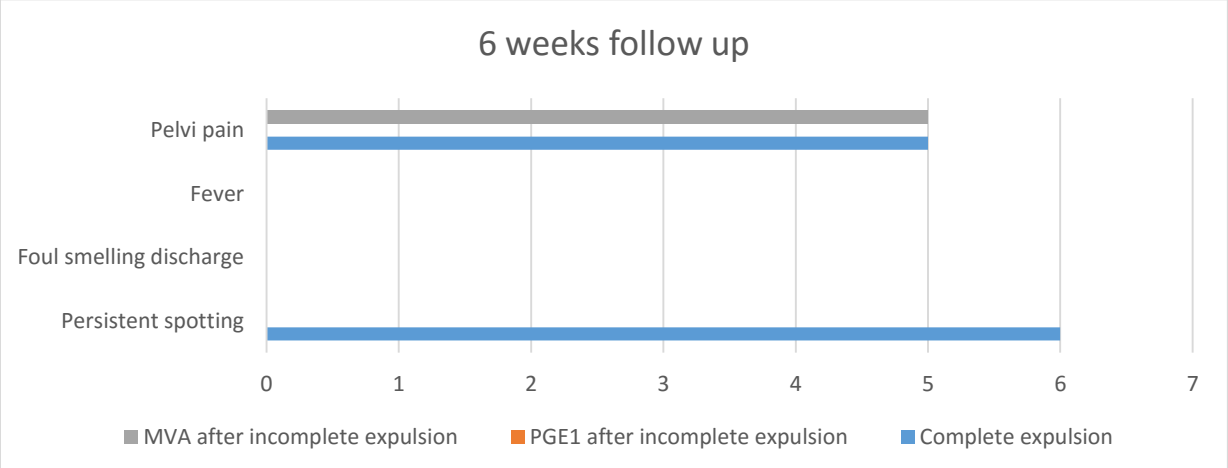
Table 22: Symptoms reported by these women are during follow up:

		No further treatment group (n=59)	Repeat PGE1 group (n=2)	MVA group (n=39)
Persistent spotting	1st week	14	1	6
	4th week	3	-	1
	6th week	6	-	-
Foul smelling discharge	1st week	-	-	-
	4th week	1	-	1
	6th week	-	-	-
Fever	1st week	-	-	-
	4th week	-	-	-
	6th week	-	-	-
Pelvic pain	1st week	5	-	2
	4th week	5	-	2
	6th week	5		2

Figure: 14


First week follow up
Pelvic pain
Fever
Foul smelling discharge
Persistent spotting
0
2
4
6
8
10
12
14
16
MVA group (39)
Repeat PGE1 group (2)
Complete expulsion group (59)


4th week follow up
Pelvic pain
Fever
Foul smelling discharge
Persistent spotting
0
2
4
6
8
10
12
14
16
MVA group (39)
Repeat PGE1 group (2)
Complete expulsion group (59)


6 weeks follow up
Pelvi pain
Fever
Foul smelling discharge
Persistent spotting
0
1
2
3
4
5
6
7
MVA after incomplete expulsion
PGE1 after incomplete expulsion
Complete expulsion

The analysis of the study was done with two sample t-test and chi square test. As the number of women with separate symptoms during follow up in each group were less, composite outcome was taken for the analysis.

Table 23: Duration of hospital stay

Duration of hospital stay	No further treatment (SD) (n=59)	Repeat PGE1 group(SD) (n=2)	MVA group (SD) (n=39)	p-value
<24 hours 24-48hours >48hours	15(25.42) 25(42.37) 19(32.2)	0(0.00) 0(0.00) 2(100.0)	5(13.16) 15(39.47) 18(47.37)	0.181

The difference in the duration of hospital stay in the three different groups was not statistically significant.

Table 24: Morbidity during hospital stay

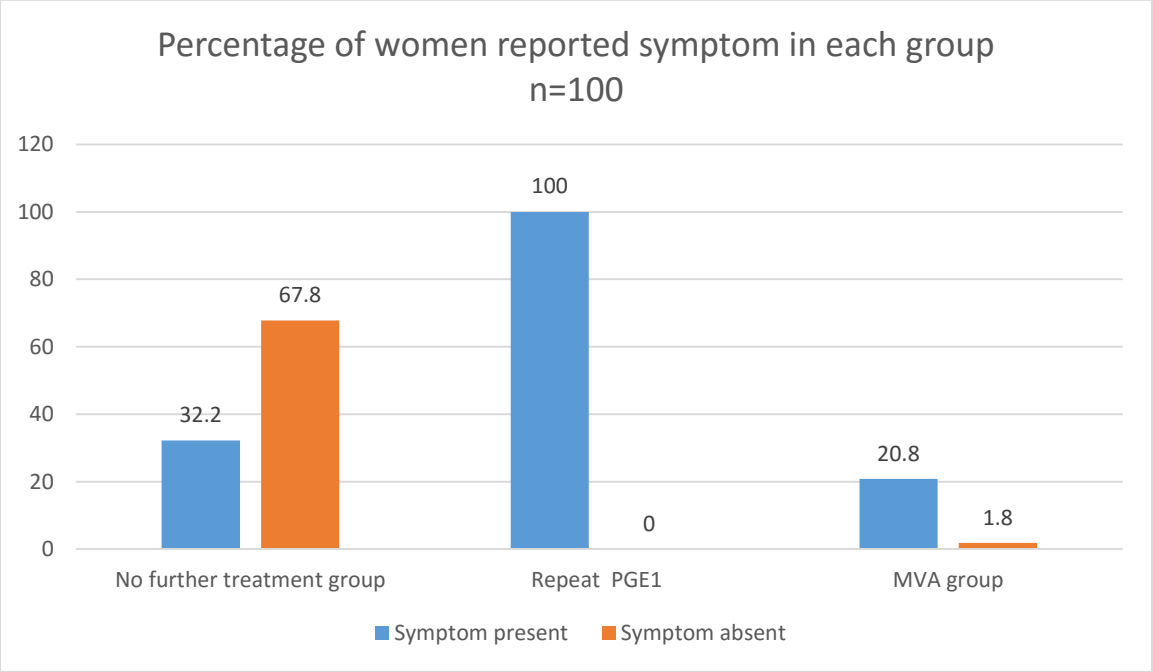
Morbidity during hospital stay	No further treatment group (SD) (n=59)	Repeat PGE1 group(SD) (n=2)	MVA group (SD) (n=39)	P-value
Yes No	0(0.00) 59(100.00)	0(0.00) 2(100.00)	2(5.13) 37(94.87)	0.203

Only two women in the MVA group had morbidities during hospital stay. One woman had fever-needed antibiotics and another had low hemoglobin needed blood transfusion.

Table 25: Composite symptoms during follow up in three groups:

Any one complication	No further treatment group (SD) (n=59)	Repeat PGE1 group (SD) (n=2)	MVA group (SD) (n-39)	P-value
Yes	19(32.2)	2(100.0)	8(20.8)	0.038
No	40(67.80)	0 (0.0)	31(79.49)	

Figure 15: Bar chart Percentage of women reported symptom in each group



As the numbers of women having symptoms during follow up period were few, composite outcome was taken for analysis. The symptoms (persistent spotting, foul smelling vaginal discharge, fever and pelvic pain) present in no further treatment group, repeat PGE1 group and MVA groups were 19, 2 and 8 respectively. The occurrence of the symptoms was statistically higher in no treatment group. (p value = 0.038).

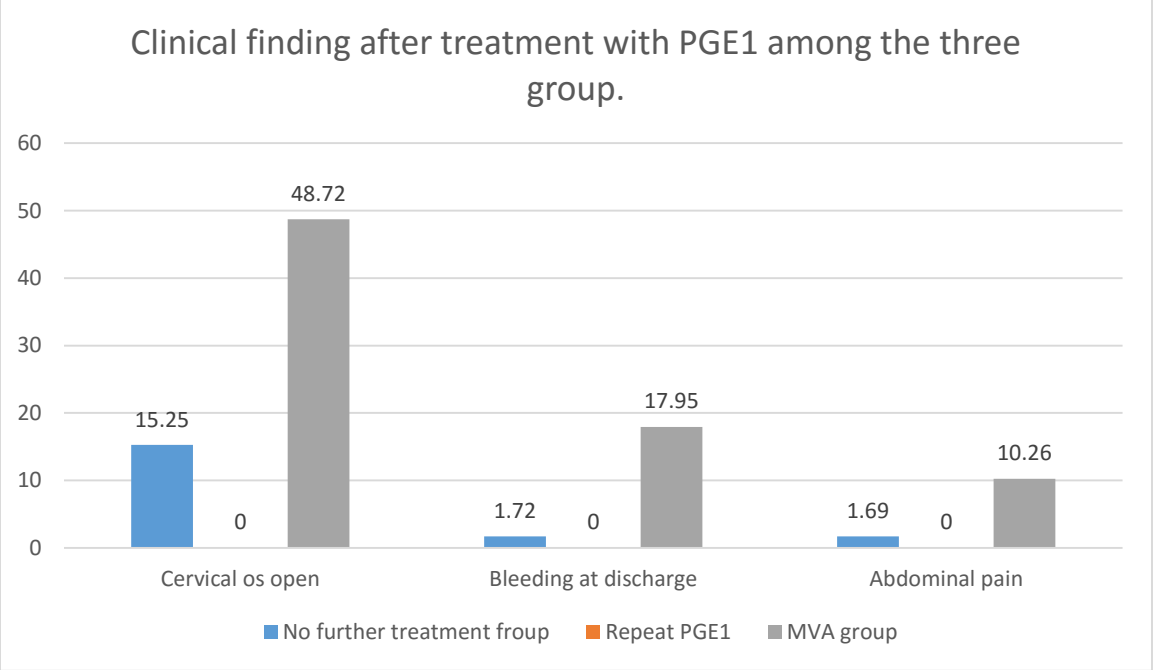
Table 26: Correlation between the clinical findings at the time of discharge among the three group of women

Per vaginal examination at the time of discharge	No further treatment group (%) (n=59)	Repeat PGE1 group (%) (n=2)	MVA group (%) (n=39)	P-value
Cervical os open Cervical os closed	9(15.25) 50(84.75)	0(0.00) 2(100.00)	19(48.72) 20(51.58)	0.01

Bleeding at the time of discharge	No further treatment group(SD) (n=59)	Repeat PGE1 group (SD) (n=2)	MVA group (SD) (n=39)	P-value
Yes No	1(1.72) 57(98.28)	0(0.00) 2(100.0)	7(17.95) 32(82.05)	0.05

Abdominal pain	No further treatment group(SD) n=59	Repeat PGE1 group (SD) N=2	MVA group(SD) N=39	p-value
Yes No	1(1.69) 58 (98.31)	0 (0.0) 2(100.0)	4(10.26) 35(89.74)	0.155

Figure 16: Correlation between the clinical findings at the time of discharge among the three group of women



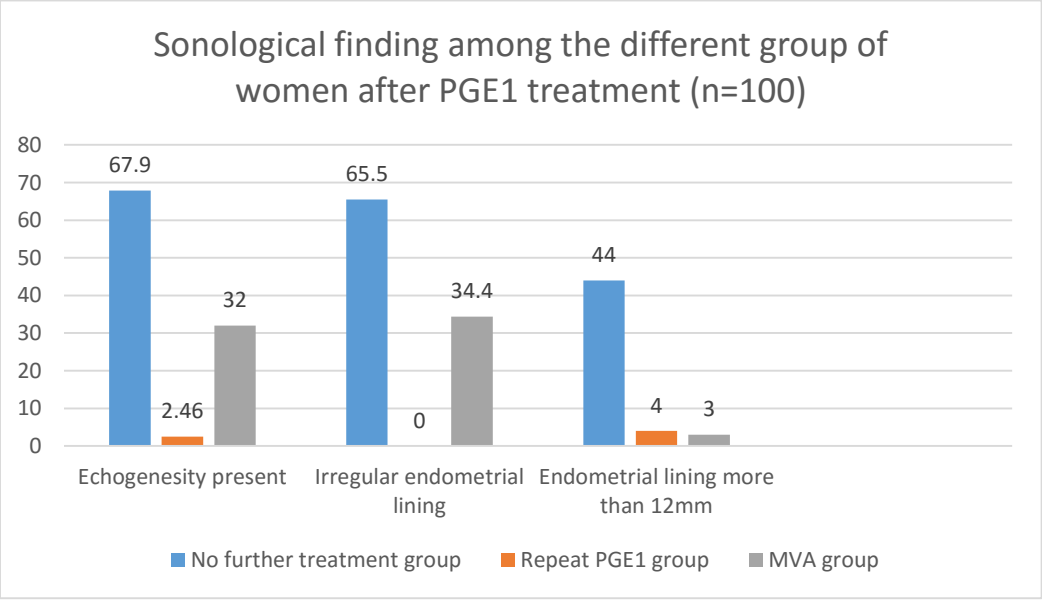
The more number of women in the MVA group had clinical findings (open cervical os, bleeding PV and abdominal pain) as compared to other groups. The difference was statistically significant for open cervical os and bleeding PV at discharge. P values were 0.01 and 0.05 respectively.

Table 27: Correlation between the Sonologic findings at the time of discharge among the three group of women:

Irregularity of the endometrial lining	No further treatment group (%) (n=59)	Repeat PGE1 group (%)(n=2)	MVA group (%) (n=39)	P-value
Present	57(96.61)	2(100.0)	36(92.31)	0.60
Absent	2(3.39)	0(0.00)	3(7.69)	

Echogenicity	No further treatment group (%) (n=59)	Repeat PGE1 group (%) (n=2)	MVA group (%) (n=39)	P-value
Present	55(93.22)	2(100.0)	26(66.67)	0.02
Absent	4(6.78)	0(0.0)	13(33.32)	

Figure 17: Sonologic findings at the time of discharge among the three group of women



As far as sonologic findings were concerned, there were no significant differences in irregularity of endometrial lining at the time of discharge among the groups. However, the presence of echogenicity was significantly higher in no treatment group (93.2% versus 66.6%, p=0.02)

Table 28: Presence of echogenicity in the uterine cavity and symptoms during follow up

USG Echogenicity	Symptoms		P-value
	Absent	Present	
Present	55(77.5)	28(96.53)	0.021
Absent	16(22.5)	1(3.5)	

In the subgroup of women with presence of echogenicity in the uterine cavity, more number of the women reported the symptoms during follow up period and the difference was statistically significantly (96.5% vs 3.5% p = 0.021).

Table 29: Endometrial thickness among the group:

Endometrial thickness(mm)	Symptom present (%)	Symptom absent (%)	p-value
<5mm	5(10.87)	2(8.0)	0.78
5-7mm	8(17.39)	5(20.0)	
8-12mm	18(39.13)	10(40.0)	
13-15mm	2(4.35)	3(20.0)	
16-25mm	10(21.74)	5(20.0)	
26-30mm	2(4.35)	0(0.0)	
>30mm	1(2.17)	0(0.0)	

For the cut off value of the different endometrial thickness there was no statistically significant difference in the symptom in follow up.

Table: 30 Median endometrial thicknesses in the two group of women

	No further treatment group (n=55) Median (IQR)	MVA group(n=21) Median (IQR)	P-value
Endometrial thickness	9(7,10)	23(13,28)	0.0009

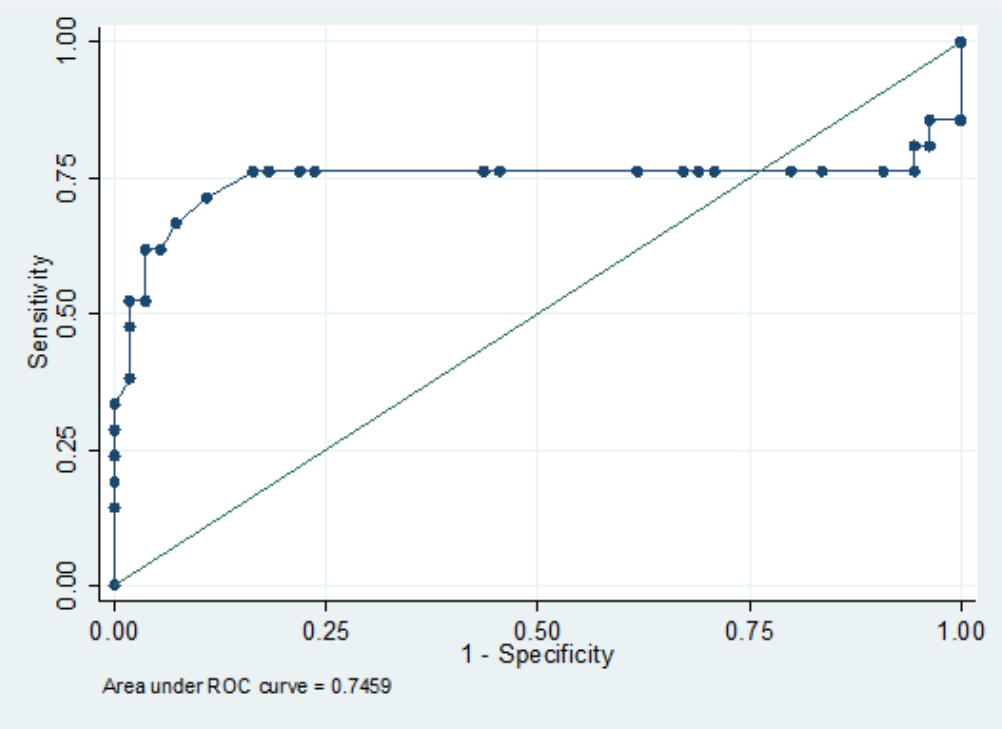
*Mann-Whitney V test used to calculate the p-value.

The median endometrial thickness of the no further treatment group was 9 mm and the women with incomplete expulsion were 23 mm. The difference was statistically significant (p=0.0009).

Table 31: Sensitivity and specificity of endometrial thickness for symptoms.

Cut point	Sensitivity	Specificity	Classified correctly	LR+	LR-
(>= 0)	100.00%	0.00%	27.63%	1.0000	
(>= .9)	85.71%	0.00%	23.68%	0.8571	
(>= 1.7)	85.71%	3.64%	26.32%	0.8895	3.9286
(>= 1.9)	80.95%	3.64%	25.00%	0.8401	5.2381
(>= 2.4)	80.95%	5.45%	26.32%	0.8562	3.4921
(>= 4)	76.19%	5.45%	25.00%	0.8059	4.3651
(>= 5)	76.19%	9.09%	27.63%	0.8381	2.6190
(>= 6)	76.19%	16.36%	32.89%	0.9110	1.4550
(>= 7)	76.19%	20.00%	35.53%	0.9524	1.1905
(>= 7.5)	76.19%	29.09%	42.11%	1.0745	0.8185
(>= 7.9)	76.19%	30.91%	43.42%	1.1028	0.7703
(>= 8)	76.19%	32.73%	44.74%	1.1326	0.7275
(>= 9)	76.19%	38.18%	48.68%	1.2325	0.6236
(>= 9.1)	76.19%	54.55%	60.53%	1.6762	0.4365
(>= 10)	76.19%	56.36%	61.84%	1.7460	0.4224
(>= 10.5)	76.19%	76.36%	76.32%	3.2234	0.3118
(>= 11)	76.19%	78.18%	77.63%	3.4921	0.3045
(>= 12)	76.19%	81.82%	80.26%	4.1905	0.2910
(>= 13)	76.19%	83.64%	81.58%	4.6561	0.2847
(>= 16)	71.43%	89.09%	84.21%	6.5476	0.3207
(>= 18)	66.67%	92.73%	85.53%	9.1667	0.3595
(>= 19)	61.90%	94.55%	85.53%	11.3492	0.4029
(>= 20)	61.90%	96.36%	86.84%	17.0238	0.3953
(>= 22)	52.38%	96.36%	84.21%	14.4047	0.4942
(>= 23)	52.38%	98.18%	85.53%	28.8096	0.4850
(>= 24)	47.62%	98.18%	84.21%	26.1906	0.5335
(>= 25)	38.10%	98.18%	81.58%	20.9524	0.6305
(>= 27)	33.33%	100.00%	81.58%		0.6667
(>= 28)	28.57%	100.00%	80.26%		0.7143
(>= 30)	23.81%	100.00%	78.95%		0.7619

Figure 18: ROC curve.



Receiver operative characteristic curve of endometrial thickness as a predictor of symptoms was generated with data in table 29. The area under the curve defines the 95% confidence interval around the ROC. X-axis (1-specificity) can be interpreted as false positive risk. The ROC curve showed the best sensitivity and specificity of the endometrial thickness to predict symptoms was at more than 12-13 mm.

Table 32: Outcome of different doses of PGE1

No of doses used	Frequency	Outcome of treatment	Number
1	15	No further treatment	7
		Repeat doses of PGE1	0
		MVA done	8
2	28	No further treatment	20
		Repeat doses of PGE1	0
		MVA done	8
3	53	No further treatment	30
		Repeat doses of PGE1	2
		MVA done	21
More than 3	4	No further treatment	2
		Repeat doses of PGE1	0
		MVA done	2

Figure: 19 Outcome of different doses of PGE1

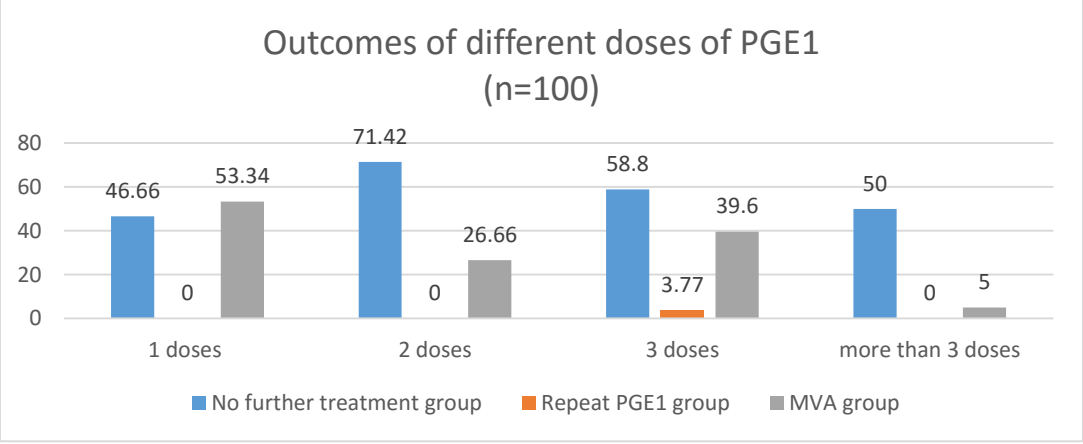


Table 33: The analysis of the outcome of two doses verses three doses of PGE

Number of doses	Symptom present (%)	Symptom absent (%)	p-value
2 3	19 (34.55) 36 (65.45)	9 (34.62) 17 (65.38)	0.09

The symptoms were more among the women who had received 3 dose of misoprostol. (65.45 % VS 34.55%, p value – 0.09) but difference was not significant.

Table: 34 The outcome of two doses verses three doses of PGE1 among different group of women

Number of doses	No further treatment group (%)	Repeat PGE1 group (%)	MVA group (%)	P-value
2 3	20(40.82) 29(59.18)	0(0) 2(100.0)	8(26.67) 23(73.33)	0.255

The number of the dose of misoprostol was not significantly difference among different groups but there was no statistically difference in the outcome.

Table 35: Resumption of menstrual cycle at the end of 6 week

Resumption of menstrual cycle at 6 weeks	No further treatment group (%)	Repeat PGE1 group (%)	MVA group (%)	p-value
Yes	39(81.25)	2(100.0)	21(67.74)	0.2
No	9(18.75)	0(0.0)	10(32.76)	

At the end of the follow up until 6 weeks, 81.2% of women in the no further treatment group had resumed the menstrual cycle as compared to 67.74% women in the MVA group. However, this difference was not statically significant.

Repeat consultation:

Among 100 women, 16 came for repeat consultation. Most of the women came for routine checkup after the early pregnancy loss. Only one woman came for persistent spotting per vagina. USG showed presence of echogenicity in the uterine cavity and she was given repeat dose of PGE1. No women required re-admission. The symptoms reported during follow up period subsided by itself without any treatment.

Table 36: Baseline characteristics in symptomatic and asymptomatic women.

Character	Symptoms absent (SD)	Symptoms present (SD)	P -value
Age (years)	26.8(4.36)	25.48(6.01)	0.213
Weight(kg)	58.59(14.45)	61.29(17.19)	0.787
Height(cm)	154.73(5.71)	155.69(6.27)	0.769
BMI(kg/m2)	24.35(5.95)	25.57(6.78)	0.812
Obstetrics score(Gravida)			
• Primi	34(47.89)	13(44.8)	0.64
• Multi	37(52.10))	15 (51.72)	
Obstetrics score(Parity)			
• Null parity	41.(57.75)	17(60.71)	0.90
• Primi parity	23(32.39)	9(3214)	
• Multiparty	7(9.86)	9(9.09)	
Blood group			
• A	12(17.14)	4(13.79)	0.654
• B	20(28.57)	10(34.48)	
• AB	7(10.00)	2(6.9)	
• O	27(38.57)	13(44.83)	
• Rh negative	4(5.71)	0	
Prev. history of MTP			
• None	51(71.83)	21(72.41)	0.56
• Once	11(15.49)	4(13.79)	
• Twice	6(8.45)	1(3.45)	
• More than twice	3(4.23)	3(4.23)	

Prev. history of PID • Yes • No	 1 1.41) 70(98.59)	 1(1.41) 28(96.55)	 0.509
Prev. history of DUB • Yes • No	 4(5.63) 67(94.37)	 3(10.34) 26(89.66)	 0.402
GA at diagnosis • >12 week • < 12 week	 59(83.10) 12(16.90)	 28(96.55) 1(3.45)	 0.069
Symptoms for admission • Spotting • Passage of tissue • Asymptomatic	 41(57.75) 2(2.82) 28(39.44)	 14(48.28) 0(0.00) 15(51.72)	 0.39
Duration of spotting at admission • No spotting • <24 hours • 24hours to 3 days • 3-7 days • >7 days	 27(38.03) 30(42.25) 9(12.68) 2(2.82) 3(4.230	 16(55.17) 7(24.14) 4(13.79) 2(6.9) 0(0.0)	 0.255
Regimen of PGE1 used • 800 mcg Q12H • 400 mcg Q6H	 66(92.96) 5(7.04)	 29(100.00) 0(0.00)	 0.143

There was no significant difference in the baseline characteristics between symptomatic and asymptomatic women.

Table 37: Logistic regression of the cofounders

Cofounders	Odds Ratio	Standard Error	[95% Conf. Interval]
• GA at diagnosis	0.097	0.105	0.01- 0.82
• Age	0.91	0.052	0.81-1.02
• BMI	1.03	0.042	0.95-1.12
• Prev. MTP	1.99	0.345	0.67-2.10
• GA at presentation	0.14	0.147	0.02-1.15
• Symptom at admission	1.11	0.280	0.67-2.10
• Number of doses used	1.01	0.320	0.56-1.82
• DUB	0.31	0.34	0.04-2.59
• PID	1.29	2.01	0.054-.34.3

DISCUSSION

In our prospective observational study, cohort of women with early pregnancy failure less than 14 weeks was admitted for termination of pregnancy with medical method.

In this study 87% of women were less than 12 weeks. About 43% of women were asymptomatic at the time of admission. Misoprostol at a dose of 800 mcg every twelve hours was the schedule used in majority of the women. 28% and 53 % of women received 2 doses and 3 doses respectively.

The Gestational age at the time of diagnosis of early pregnancy failure and at the time of admission for termination of the pregnancy had no effect on the outcome. Patient age, BMI, parity, past pregnancy failure or past history of PID or DUB did not influence the success rate or symptom on follow up.

In our study complete expulsion was diagnosed in 59% of women who then were not given any further treatment before discharge. 41% of the women needed further management and among this manual vacuum aspiration was the choice in 39% of women and only two women had repeat doses of misoprostol. As the numbers of women treated with repeat doses of PGE1 were only two, hence the composite outcome essentially was between the no further treatment group and the MVA group.

Presence of persistent spotting (less than 4-5 pad) at the time of discharge was less in women to whom no treatment was given (1 out of 59) compared to women who had

incomplete expulsion and underwent MVA (7 out of 39). The difference was statistically significant. (P value =0.05). However, this symptom subsided itself over weeks' time without any intervention. Similar result was also shown by Trinder et al and Neilsen et al (44) (81).

Among the 59% of women who did not have any treatment a significant number of women had persistent spotting compared to women who underwent MVA (32.2% versus 20.8% p value=0.038). However, none of these women needed readmission or curettage and symptoms subsided by its own without any intervention by six weeks.

Spontaneous resumption of the cycle by 6th week was seen in 80% of the women in no further treatment group and 68% in MVA group. However, the difference is not statistically significant; a trend towards delay in resumption of the cycles within six weeks would need evaluation in larger study.

The group of women that needed manual vacuum aspiration bleeding was the commonest cause for performing MVA. The symptoms were much lesser than the group that had no further management.

The distribution of different blood group in Indian population as reported by a multi centric study that O was the most common blood group (37.12%) followed by B and A 32 and 26% respectively. While AB was the least prevalent group at 7.74%. 94.61% of the population was Rh positive and the rest were Rh negative. (82) The distribution of blood group was similar in the study cohort.

The analysis of clinical examination has shown that more women with MVA group 18% vs 2% (p value=0.05) had bleeding and open cervical os (48.7% vs 15.3% p value = 0.01) as compared to no further treatment group. This finding only suggests that the above symptoms were reasons for performing the MVA.

In the subgroup of women with presence of echogenicity in the uterine cavity, more number of women reported symptom at follow up period (96.5% vs 3.5%). The difference was statistically significant (p value =0.02). Similar finding was also shown by Debby et al 2007 in the retrospective study of sonographic appearance after first trimester uterine evacuation (78)

Although the difference in the irregularity in the endometrial lining was not statistically significant among the different group of women (96.6% vs 92.3% p value=0.6). However, none of these women needed further treatment on follow up. Irregularity of the endometrial lining and echogenicity were significantly increased in the women of no further treatment group.

The median value of endometrial thickness in women who did not receive further treatment was 9 mm (IQR 7, 10) and in women who underwent MVA was 23mm (IQR 13, 28). The difference in the finding was statistically significant. This result is consistent with Mathew et al 2007 (71) and Cetin et al 2004 (83).

In our study, we compared the ROC-AUCs of the endometrial thickness among the three group of women. At the endometrial thickness of 12mm the sensitivity and specificity for diagnosis the occurrence of symptom after discharge is 76.19% and 81.82% respectively.

At the endometrial thickness of 13 mm the sensitivity and specificity for diagnosing the occurrence of symptom after discharge is 76.19% and 81.64% respectively.

Prior studies have proposed different cut off for endometrial thickness to facilitate the diagnosis of incomplete expulsion. In the study of 33 women by Alcazar et al (69), a cut off value of 12 mm endometrial thickness was proposed with sensitivity of 75% and specificity 62.5%. In the retrospective study by Nielson and Hahlin et al (4) the cut off was proposed as 15mm. Hence, Leung et al (72) and Wolman et al (76) have proposed that a combination of clinical and ultrasound finding should be used to diagnose the incomplete evacuation and need for further management.

No statistically significant difference in the outcome of women who were received different doses of misoprostol for treatment.

CONCLUSION

1. The overall success of termination of early pregnancy loss with medical method is 59% and the outcomes are not affected by the age, gestation age, BMI or symptom before termination, previous history of MTP, PID or DUB.
2. The outcomes are not related to the Misoprostol dosage regimen used or the number of dosage used.
3. The women who were presumed to have complete expulsion after medical method may have persistent symptom for variable duration till 6 weeks, but none of the symptom are severe enough requiring readmission or physician consultation and subside itself without any intervention over a period of 1-2 week.
4. After treatment with misoprostol presence of spotting per vagina (17.9% vs 1.72 % p value= 0.05) with or without abdominal pain, and presence of the echogenicity in ultrasound examination (93.2% vs 66.7% p value = 0.02) are the predictor of persistent of symptoms.
5. The cut off measurement of endometrial thickness for diagnosis of persistence of symptom is 12-13mm with sensitivity of 76.19% and specificity of 83.64%. However, its use in clinical practice is questionable

6. Absence of sac in the uterine cavity irrespective of the endometrial thickness and echogenicity in the absence of significant bleeding suggest complete expulsion.
7. Menstrual cycle resumed in 81.2% in the no further treatment group and 67.74% in the MVA group (p value 0.02) by the end of 6 weeks.

LIMITATIONS

1. This is an observational study and hence bias cannot be ruled out.
2. We could not complete the sample size and hence the exact outcome cannot be commented upon.
3. As the number of women in each groups were few, only the composite outcome of the symptoms of all the three period (i.e. 1st week, 4th week, 6th week) were taken for analysis.
4. Long term follows up was not possible in this study hence complication like intra uterine adhesion could not be studied.
5. There were few women in the repeat doses group and hence comparison was essentially between no further treatment and MVA group.

ANNEXURE

BIBILIOGRAPGY

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INFORMATION SHEET

Title: A prospective observational study of the follow up of medical management of early pregnancy failure.

Early pregnancy failure is a condition usually confirmed by ultrasound scan. In this condition, women present with absence of menstruation with or without spotting per vagina. Ultrasound in these women shows a gestational sac in the womb with tiny fetus in absence of heart beat or the womb with an empty sac. Both these conditions eventually need termination. The mode of intervention is either expectant waiting for spontaneous expulsion or use medicines or curettage to terminate pregnancy. In our institution we use medical management with misoprostol in doses recommended by the World Health Organization. If the decision for medical management is taken, we would like to include you in our observational study.

In this study we will note your symptoms and scan findings before the decision for termination. The number of doses, the need for curettage and other decisions will be done by your treating physician. We will note the clinical and radiological findings till discharge and follow you up telephonically for a period of 6 weeks. In this duration we will note your symptom and follow up if any intervention or admission is required.

You are invited to participate in above study. You will have no risk or benefit by participating in the study. However, your decision to participate will not affect your

routine standard of care. You are always having the option to withdraw from the study without any change in your medical care.

CONSENT

Study name: A prospective observational study of the follow up of medical management of early pregnancy failure.

Study number:

Subject name:

Hospital number:

Age:

Date:

Address and phone number:

1. I confirm that I have read and understood the information sheet dated ……. for the above study and had the opportunity to ask question and further examination. ( )
2. I understood that participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or rights being affected. ( )
3. I understand that the sponsor of clinical study, the ethic committee and the regulatory committee will not need my permission to look at my health records both in respect to current study and any further research that may be conducted in relation to it, even if I

withdraw from the trial. I agree to this assess. However, I understand that my identity will not be revealed in any information released to third parties or published. ( )

4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for the scientific purpose(s) ( )
5. I agree to take part in this study. ( )

Signature (or thumb impression) of the subject /legally acceptable representative……

Date…….

Signatory's name: ……

Signature of the investigator: …….……

Date: …….

Study investigator's name…….

Signature of the witness…….

Date: ……..……..

Name of the witness: …….

CLINICAL RESEARCH FORM

A prospective observational study of the follow up of medical management of early pregnancy failure:

1. Serial number
2. Name:
3. Hospital number:
4. Date:
5. Address and phone number:
6. Age (in years)
7. Obstetric score:
8. Blood group: ABAB.O Rh Negative
9. BMI:
10. Height (cm)
11. Weight (kg)
12. H/O Prev. MTP
    1. None
    2. Once
    3. Twice
    4. More than twice
13. LMP:

14. GA at presentation:
    1. Less than 12 week
    2. More than 12 week
15. USG at the time of diagnosis
    1. Gestational sac: Regular/ Irregular
    2. CRL
16. Indication for termination:
    1. Anembryonic gestation:
    2. Embryonic/early fetal demise
17. Symptom prior to admission
    1. H/O Spotting/Bleeding past 24 hour/past 1 week
    2. H/O Passage of tissue
    3. Asymptomatic
18. GA at admission:
    1. Less than 9 week
    2. 9-13 week
    3. More than 13 week
19. Duration of spotting
    1. No spotting
    2. <24 hour
    3. 24 hour to 3 days
    4. 3 days to 7days

5. >7 days Regimen of PGE1

20. Induction to expulsion interval

21. Numbers of dose:

22. Abdominal pain after expulsion before discharge

    1. Yes
    2. No

23. Vaginal examination –

    1. Cervical Os (after expulsion before discharge) Open Close
    2. H/O bleeding >4-5 pad per day (before discharge) Yes.No

24. US finding (after expulsion)

    1. Endometrial thickness in mm:
    2. Echogenicity of the content:
        i. Yes
        ii. No
    3. Irregular endometrial lining:
        i. Yes
        ii. No

25. Repeat doses of misoprostol used.

    1. Yes
    2. No

26. Curettage done following expulsion:

    1. Yes

2. No

27. If yes reason:

    1. Persistent bleeding
    2. ultrasound finding
    3. Physician decision

28. US finding after curettage (if done)

    1. Yes
    2. No

29. If yes USG finding:

    1. Endometrial thickness in mm:
    2. Echogenicity of the content:
        i. Yes
        ii. No
    3. Irregular endometrial lining:
        i. Yes
        ii. No

30. Total duration of hospital stay.

31. Any morbidity during hospital stay period:

    1. Yes
    2. No

32. Prev. history of DUB

    1. Yes

2. No

33. Prev. history of PID:

    1. Yes
    2. No

34. FOLLOW UP:

35. Persistent spotting

    1. @ 1 week: Yes No
    2. @4 weeks Yes No
    3. @ 6 weeks Yes No

36. Foul smelling discharge

    1. @1 week Yes No
    2. @4 weeks Yes No
    3. @ 6 weeks Yes No

37. Fever

    1. @ 1 week Yes No
    2. @4 weeks Yes No
    3. @ 6 weeks Yes No

38. Pelvic pain

    1. @ 1 week Yes No
    2. @ 4 weeks Yes No
    3. @ 6 weeks Yes No

39. Resumption of cycle at the end of 6 week

1. Yes
2. No

40. Repeat consultation or admission
    1. Yes
    2. No

41. If yes reason:
    1. Persistent spotting
    2. Foul smelling discharge
    3. Fever:
    4. Pelvic pain
    5. Check up

42. Repeat USG done at readmission/consultation:
    1. Yes
    2. No

43. If yes finding:
    1. Endometrial thickness
    2. Echogenicity of the content
    3. Endometrial lining: Regular / Irregular

44. Treated With
    1. Curettage
    2. Antibiotics
    3. Hormones

45. Indication:

    1. Persistent bleeding
    2. Ultrasound finding
    3. Physician decision

46. Histological examination done:

    1. Yes
    2. No

47. Histological report:

    1. Deci dual tissue
    2. Chorionic tissue

MASTER SHEET

serno	da	ag	gr	pa	li	sb	ab	de	bg	bmi	ht	wt	premtp	lmp	gapres	usgatdiage	usgatdiacr	indterm	symprtoadm	gaadm	durspot
1	12/11/2015	22	2	1	1	0	0	0	4	29.3	160	75	1	22/08/2015	1	1	18	1	3	2	2
2	13/11/2015	25	4	1	0	0	2	1	4	25.2	150	57	3	21/08/2015	1	1	90	1	1	2	5
3	18/11/2015	34	3	2	2	0	0	0	3	52.7	150	118.7	1	02/09/2015	1	1	36	1	1	2	2
4	20/11/2015	32	2	1	0	1	0	0	3	21.9	157	54.1	1	28/09/2015	1	1	8.5	2	1	1	5
5	07/12/2015	42	3	0	0	0	2	0	2	25.2	145	53	3	31/08/2015	2	1	0.77	1	3	3	2
6	08/12/2015	33	8	1	1	0	6	0	4	22.8	160	58.5	4	16/09/2015	1	1	0	1	1	2	3
7	11/12/2015	26	1	0	0	0	0	0	2	22.8	162	60	1	21/09/2015	1	1	50	1	3	2	1
8	17/12/2015	30	2	0	0	0	1	0	2	21.3	150	48	2	19/10/2015	1	2	0	1	3	1	2
9	19/12/2015	24	1	0	0	0	0	0	4	17.8	155	43	1	03/10/2015	1	1	17	2	1	2	2
10	21/12/2015	20	1	0	0	0	0	0	2	20.9	156	51.2	1	17/09/2015	1	2	41	1	3	3	1
11	24/12/2015	30	4	1	0	1	2	0	2	20.4	150	46	3	24/10/2015	1	2	0	1	1	1	5
12	01/01/2016	34	2	1	1	0	0	0	4	23.6	152	54.6	1	09/11/2015	1	1	11.4	1	1	1	2
13	05/01/2016	26	1	0	0	0	0	0	1	23	146	49.2	1	03/11/2015	1	2	0	1	1	1	2
14	13/01/2016	25	1	0	0	0	0	0	4	28.8	150	65	1	16/10/2015	2	2	17	1	3	2	2
15	13/01/2016	30	2	0	0	0	1	0	4	24.4	159	61.8	2	01/11/2015	2	1	0	1	1	3	3
16	13/01/2016	23	3	2	1	0	0	1	2	15.6	165	42.7	1	25/10/2015	1	1	12.3	1	3	2	1
17	14/01/2016	23	1	0	0	0	0	0	4	26.6	162	70	1	29/10/2015	1	1	4.1	2	1	2	2
18	16/01/2016	27	2	0	0	0	1	0	1	23.6	154	56	2	27/10/2015	1	2	10.4	1	3	2	1
19	20/01/2016	26	4	2	2	0	1	0	2	23.6	146	49.6	2	17/10/2015	1	1	50	1	1	3	2
20	21/01/2016	20	3	1	1	0	1	0	1	20.2	145	42.4	2	01/11/2015	1	1	11	2	2	2	3
21	29/01/2016	30	1	0	0	0	0	0	5	17.3	154	41.2	1	04/11/2015	1	2	0	2	1	2	2
22	01/02/2016	25	1	0	0	0	0	0	2	18.1	150	42	1	23/11/2015	1	1	0.6	1	3	2	1
23	03/02/2016	29	1	0	0	0	0	0	4	28	158	70	1	10/11/2015	1	2	7.7	2	1	2	2
24	05/02/2016	28	3	2	1	0	0	1	4	21.1	151	48.2	1	14/11/2015	1	1	8	1	1	2	2
25	05/02/2016	23	2	1	1	0	0	0	4	24.9	158	62.2	1	30/11/2015	1	1	7	1	1	2	3
26	10/02/2016	24	2	1	0	1	0	0	2	29.2	148	63.9	1	16/11/2016	1	1	63	1	3	2	1
27	13/02/2016	24	2	1	1	0	0	0	3	12.4	158	31	1	23/11/2015	1	1	7.2	1	1	2	2
28	17/02/2016	21	2	1	1	0	0	0	1	31.1	158	77.7	1	15/11/2015	1	2	0	1	1	1	4
29	18/02/2016	30	2	1	1	0	0	0	3	31.6	164	85	1	03/12/2015	1	2	0	1	3	2	1
30	18/02/2016	22	6	1	1	0	4	0	2	26.8	143	55	4	14/12/2016	1	2	0	1	3	1	1
31	18/02/2016	23	1	0	0	0	0	0	4	22.8	148	50	1	26/11/2016	1	2	0	1	1	2	2
32	20/02/2016	25	2	0	0	0	1	0	4	24.2	160	62	1	09/11/2016	2	1	19	2	1	3	4
33	22/02/2016	22	1	0	0	0	0	0	2	37.7	150	85	1	29/12/2015	1	1	0	1	1	1	3
34	22/02/2016	23	1	0	0	0	0	0	4	22.8	156	55.6	1	04/12/2015	1	1	0	1	3	2	1
35	25/02/2016	22	1	0	0	0	0	0	4	20.8	160	53.3	1	26/11/2016	1	1	0	1	3	2	1
36	02/03/2016	27	2	1	1	0	0	0	2	19.5	160	50	1	14/12/2015	1	1	30.4	2	1	2	3
37	03/03/2016	17	1	0	0	0	0	0	4	18.2	158	45.5	1	10/12/2015	1	1	8.7	1	3	2	1
38	03/03/2016	23	1	0	0	0	0	0	4	22.8	156	55.6	1	04/12/2015	1	1	51	1	3	2	1
39	06/03/2016	35	5	1	1	0	3	0	5	27.4	154	65	4	10/01/2016	1	1	6	1	1	1	2
40	07/03/2016	26	2	0	0	0	1	0	1	25.1	148	55	2	18/12/2015	1	1	17	1	3	2	1
41	07/03/2016	21	1	0	0	0	0	0	1	16.7	159	42.3	1	11/12/2015	1	2	0	1	1	2	3
42	08/03/2016	25	3	0	0	0	2	0	1	28.6	158	71.5	3	16/12/2015	1	1	0	1	3	2	1
43	08/03/2016	27	3	1	1	0	1	0	4	29	154	68.9	2	01/01/2016	1	1	12	1	2	1	3
44	11/03/2016	23	5	1	1	0	3	0	2	26.6	150	60	3	27/12/2015	1	1	0.45	1	1	2	2
45	11/03/2016	26	1	0	0	0	0	0	4	32.4	162	85.2	1	15/12/2015	1	1	12	1	1	2	1
46	14/03/2016	31	2	1	0	1	0	0	1	21.9	156	53.3	1	27/12/2015	1	1	0	1	1	2	1
47	14/03/2016	23	1	0	0	0	0	0	2	17.9	161	46.5	1	12/01/2016	1	1	8.5	2	1	1	2
48	15/03/2016	31	2	1	1	0	0	0	2	31.1	160	79.8	1	01/01/2016	1	1	0	1	1	2	3
49	16/03/2016	27	1	0	0	0	0	0	5	24.3	160	62.3	1	16/12/2015	1	1	35	1	1	2	2
50	16/03/2016	27	2	0	0	0	1	0	4	22.2	146	47.5	2	21/12/2015	1	1	0	1	1	2	4

reg	indtoexp	num	abdpain	vag	bld45	usf	usaftexpen	usaftexpec	usaftexpe1	rpt	cur	rea	per	ult	phy	usaftcur	ifdone	usecho	usirr	stay	mor	ye
1	26	3	2	2	2	1	1.9	2	2	2	2					2				60	2	
1	30	3	2	2	2	1	0.9	2	2	2	2					2				40	2	
1	80	3	2	2	2	1	0.9	2	2	2	2					2				76	2	
1	48	3	2	2	2	1	22	2	2	2	2					2				72	2	
1	6	1	2	1	2	2				2	1	1	1	2	2	1	22	1	1	26	2	
1	36	3	2	1	2	1	28	1	2	2	1	3	2	2	1	2				72	2	
1	48	3	1	1	2	1	2.4	1	1	2	1	1	1	2	2	2				76	2	
1	12	2	2	2	2	1	10	2	2	2	2					2				24	2	
1	36	3	2	2	2	2				2	2					2				49	2	
1	80	3	2	2	2	2				2	2					2				72	2	
1	24	2	2	2	2	1	20	2	2	2	1	1	1	2	2	2				36	1	fever,on an
1	72	3	1	1	1	1	30	1	1	2	1	1	1	1	2	2				72	2	
1	40	3	2	2	2	2				2	2					2				72	2	
1	40	3	2	2	2	1	19	2	2	2	2		2			2				72	2	
1	30	2	2	1	2	1	8	2	2	2	2					2				72	2	
1	36	3	2	1	2	1	10	2	2	2	2					2				48	2	
1	30	2	2	2	2	1	24	1	1	2	1	1	1	1	2	2				96	2	
1	36	3	2	1	2	1	7.9	2	1	2	2					2				40	2	
1	14	1	2	1	1	1	99.99	1	1	2	1	1	1	2	2	2				72	2	
2	36	4	2	2	1	1	25	1	2	2	2					2				24	2	
1	36	3	2	1	1	1	20	1	2	2	1	1	1	1	1	2				48	2	
1	24	2	2	2	2	1	9	2	2	2	2					2				36	2	
1	72	3	2	2	2	1	13	1	1	2	1	1	1	2	2	2				96	2	
1	24	1	1	1	1	2				2	1	1	1	2	1	1	9	2	2	48	2	
1	72	3	2	2	2	1	10	2	2	2	2					2				72	2	
1	12	2	1	1	1	1	99.99	2	2	2	1	1	1	1	2	2				24	1	1 unit blooc
2	48	6	2	2	2	1	18	1	1	2	1	2	2	1	2	2				50	2	
1	20	2	2	2	2	1	18	2	2	2	2					2				24	2	
1	22	2	2	2	2	1	16	1	2	2	2					2				48	2	
1	24	2	2	1	2	1	9	2	2	2	2					2				24	2	
1	36	2	2	1	2	1	10	2	2	2	2					2				48	2	
1	48	3	2	2	2	1	5	2	2	2	2					2				48	2	
1	24	2	2	1	2	2				2	1	1	1	2	2	2				30	2	
1	144	3	2	2	2	2				2	1	2	2	1	1	2				72	2	
1	48	2	2	2	2	1	5	2	2	2	2					2				48	2	
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dub	pid	per1	pers	persp	fou	fous	fousm	fe	fev	fer	pel	pelv	pelpa	resm	prt	ifrea	rptusg	finen	ec	re	tret	ind	hispath	hisrep
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66	26/04/2016	32	1	0	0	0	0	0	2	39.4	152	91.2	1	22/01/2016	1	1	18	1	3	2	1
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68	04/05/2016	23	1	0	0	0	0	0	4	22.1	158	55.4	1	19/02/2016	1	1	0	1	1	2	3
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77	20/05/2016	24	4	2	1	1	1	0	4	22	152	51	2	01/03/2016	1	1	0	1	3	2	1
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